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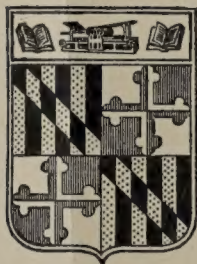
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# BULLETIN

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## CLINICAL AND EXPERIMENTAL STUDIES UPON THE INJECTION OF ALCOHOL INTO THE GASSERIAN GANGLION FOR THE RELIEF OF TRIGEMINAL NEURALGIA.\*†

By CHARLES METCALFE BYRNES, M. D.,

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### INTRODUCTION.

Nearly 200 years ago Fothergill, an English physician, described a peculiar, painful affection of the trigeminal nerve, which has since been variously designated as Fothergill's neuralgia, epileptiform neuralgia, tic douloureux and prosopalgia. Since none of these terms is distinctive, there still exists some confusion as to just what is meant by trigeminal neuralgia, and I wish to make it clear that in this monograph trigeminal neuralgia and its synonyms are used to designate a painful affection of one or more branches of the fifth cranial nerve, which is characterized by neuralgic attacks, usually of short duration, occurring spontaneously or induced by various forms of peripheral irritation, and in which the etiology and pathology are undetermined.

\* From the Departments of Clinical Neurology, Anatomy, and the Hunterian Laboratory of Experimental Surgery.

† Presented in part before the Philadelphia Neurological Society, October 24, 1913, and The Johns Hopkins Hospital Med. Soc., November 17, 1913.

From the earliest recognition of the disease up to the present time medical minds have been engaged in an effort to discover an effective and harmless method of treatment. Drugs have been, and are still, used with a certain measure of success. Minor operative procedures were then adopted in which the affected branch was sectioned and its foramen closed with various foreign substances; or occasionally destructive chemical solutions were injected into the exposed nerve or its proximal stump. While these measures were, in general, more successful than medical treatment, the relief was only temporary and often of very short duration. And lastly, with the hope of securing permanent results, the major operation for removal of the ganglion and the simpler avulsion of its sensory root were adopted. Except in the hands of the most skillful operator, the mortality following either of these operations is so high that they are not to be urged except in the more desperate cases, and as a means of last resort. Even this more extensive operation has occasionally been followed by recurrences, or has procured only temporary relief.



This, then, was the state of knowledge when Schlösser, an ophthalmologist of Munich, discovered, almost by chance, that the subcutaneous injection of 70 per cent or 80 per cent alcohol into or about the trunk of the offending nerve afforded a prompt and safe means of relief. Unfortunately, Schlösser's earliest account of his method and technique was recorded in the almost inaccessible proceedings of the *Deutsche Ophthalmologische Gesellschaft* at its thirty-first meeting in Heidelberg, September, 1903. It was not until 3 years later that his method became generally known through the publications of Levy and Baudouin, in France, who modified slightly the original Schlösser technique. Somewhat later Ostwald introduced an entirely different method of approach to the basal foramina which, however, has not been widely used. It was not long before this new treatment found its way into England, Germany, and America through the studies of Harris, Offerhaus, Kiliani, Patrick, Hecht, Grinker, and others, most of whom adopted the modified method of Levy and Baudouin.

Sufficient time has now elapsed since the introduction of this method to leave little doubt concerning its value as a means of temporary relief in the treatment of this distressingly painful affliction. Its advantages, disadvantages, complications, and difficulties have all been thoroughly reviewed by earlier advocates of the method; and 5 years' personal experience with deep intraneural injections, in which the operation has been performed several hundred times, has convinced me that of all peripheral operations it is the one of choice. Clinically, the results are all that could be desired; the operation is practically without danger; a general anesthetic is not required; there is no disfigurement; in most cases the deep foramina are readily accessible; and a successful injection is followed by complete physiological neurectomy with relief of pain for a period of from 6 months to 4 years.

It is not surprising that these gratifying clinical results are obtained, when it is recalled that Finkelnburg, Levy and Baudouin, Brissaud, Déjerine and more recently Gordon,<sup>1</sup> have shown, experimentally, that the injection of alcohol into a nerve trunk produces not only a physiological blocking of impulses, but an actual degeneration of the nerve from the point of injection to the periphery. The end result, then, is in reality, a chemical neurectomy; and while the condition following this method of destruction is more favorable for regeneration than after a cutting operation, since there is no actual break in anatomical continuity, I think it may be safely stated that, in general, the average period of relief is quite equal to that following the more extensive procedure.

It would be instructive to review briefly the several methods which have been devised for reaching the foramen rotundum and foramen ovale; since it is through these studies that a successful approach to the ganglion has been evolved, but I shall not enter into the details of technique at the present writing.

In spite of the many advantages which this new method possessed, it soon became apparent, from the study of many hundred cases, that it, like all peripheral operations, was beset with certain objectionable features. The necessary pain ac-

companying the operation, the uncertainty of success from any one injection and the almost inevitable recurrence, left much to be desired by both patient and physician. Even though the relief were temporary, many patients would, no doubt, accept the treatment more readily if they could be assured of success from a single injection. The thought of repeated injections with only temporary relief is, to some patients, almost as painful as the disease itself. Since these uncertainties could not well be overcome, the thoughtful student could only hope to become either more skillful in his technique or else adopt more radical measures.

With the destructive effect of alcohol clearly established, and the demonstration of several fairly accurate methods of approach to the foramen ovale, it is not surprising that the speculative instinct began to consider the possibility of injecting chemical substances directly into the Gasserian ganglion. It was hoped that by this means its partial destruction might be accomplished and in this way, if not a permanent cure, at least more lasting relief might be brought about.

Chemical destruction of the Gasserian ganglion has had a rather interesting evolution, and while no doubt such a procedure received its first stimulus from the earlier use of osmic acid in the destruction of peripheral nerves, it was not until after the appearance of Schlösser's contribution that any serious investigations were made in this direction. Since this time, the subject has been studied from both the clinical and experimental point of view, and it will be instructive to review the work which has been done by these two methods of investigations.

#### METHODS OF INJECTING CHEMICAL SUBSTANCES INTO THE GASSERIAN GANGLION IN MAN.

It would require more than a just apportionment of space to enter into the details of the several methods by which these injections have been made, and I shall merely indicate them by an arrangement of the material in the following order:

*Direct Injection by Exposure of the Ganglion.*—According to Simons,<sup>2</sup> one of the earliest recorded attempts to inject the ganglion by this route was made by Rasoumowsky, who, in 1910, infiltrated the exposed ganglion with a few cubic centimeters of diluted alcohol. The post-operative and clinical results are not referred to, and I have been unable to obtain the original article. Härtel, in 1912, found it necessary to employ this technique in one case, in which earlier surgical interference precluded the adoption of less radical measures.

Within the following year, Alexander and Unger<sup>3</sup> after making several unsuccessful attempts to inject the ganglion by the subcutaneous method, exposed it by the temporal route, in one case, and injected it with alcohol, *in situ*. Local anesthesia was used up to the stage of injection, when slight general narcosis was induced. The entire ganglion was not exposed, but only its anterior border near the origin of the second and third branches, in which pain had been experienced. With a fine needle, a few drops of novocain solution were injected in the neighborhood of the affected branches, and followed by the introduction of a few drops of 80 per cent



alcohol in different parts of the ganglionic area. Recovery was uneventful. The authors felt that by this procedure the following advantages had been obtained: The injection can be limited to that portion of the ganglion from which the affected branch arises; the operation, as compared with extirpation, is shortened since ligation of the artery is not necessary; hemorrhage is reduced; cerebral trauma is lessened; and by fractional injection the cornea may be spared. The logic of these deductions will be discussed in the conclusion of my paper.

*Injection Through the Exposed Foramen Ovale.*—I believe it is generally acknowledged that Wright,<sup>4</sup> in 1907 was the first to inject a chemical substance into the ganglion of a living patient. By the above method, a few drops of a 2 per cent solution of osmic acid were injected into the ganglia of 2 patients suffering from trigeminal neuralgia. One of the patients, in whom apparently all three branches were affected, had experienced some pain in the first division a few months after the operation, while the second patient had remained well up to the publication of his paper months later. In 1910, employing a similar procedure, Sicard injected 1 cc. of 80 per cent alcohol into the ganglion of a patient suffering from trigeminal neuralgia. Following the operation there was relief of pain for about 8 months (Simons).

*Subcutaneous Injection of the Ganglion.*—It was not long after the introduction of Schlösser's subcutaneous approach to the basal foramina before students of this subject began to recognize the possibility of employing this method for injecting the ganglion itself. In fact, suggestions of this nature were made as early as 1906 by Ostwald, and later by Sicard, Fransen, and others; and experimental studies in this direction were soon forthcoming.

Chollin, in 1907, by the intrabuccal method of Ostwald, introduced a needle through the foramen ovale into the ganglion of cadavers and injected methylene blue. Two years later Harris<sup>5</sup> performed similar experiments by the extrabuccal route of Levy and Baudouin, and found the coloring matter not infrequently reached the ganglion by diffusion even when the injection was made just within the foramen ovale. During my preliminary practice upon cadavers, in 1909, for acquiring the several varieties of technique for giving deep injections, it was clearly demonstrable that the ganglion is quite accessible through the foramen ovale by any one of the three methods (Schlösser, Ostwald, Levy-Baudouin), which had been described for making deep injections of the mandibular nerve. Although I did not inject coloring matter into the ganglion, the location of my needle was verified in each instance, by dissection. Offerhaus,<sup>6</sup> in 1910, also performed successful injections of the ganglion with methylene blue and referred to the probable clinical application of this anatomical knowledge.

Within the following year Pussep<sup>7</sup> made the first, although unsuccessful, attempt to inject the ganglion in a living subject. He employed the technique described by Ostwald for reaching the foramen ovale. Following the injection of alcohol, however, there occurred vomiting, cyanosis, slowing of the pulse, and headache of such severity that he regarded

them as distinct contraindications to a repetition of this form of treatment.

Four months later Taptas,<sup>8</sup> of Constantinople, recorded, so far as I have been able to ascertain, the first successful subcutaneous injection of alcohol into the ganglion of a patient suffering with trigeminal neuralgia. Strangely enough, as the author confesses, the injection was purely accidental. His original intention was to make a deep injection for the third branch according to Sicard's technique, which is practically identical with that of Levy and Baudouin. Much to his surprise, upon withdrawal of the needle, there were evidences of disturbed sensation throughout the entire trigeminal distribution. In a second case he employed the same technique with equally satisfactory results; and the patient, when seen 2 months later was still free of pain. His third case is interesting because of his failure to reach the ganglion by the above route, which necessitated the adoption of a different method of approach in which he was successful. The needle was introduced below the malar bone at a point selected by Schlösser for injecting the second or third division, and the procedure in many respects was similar to that which has since been known as Härtel's method.

Coincidentally, with the studies of Taptas, similar investigations were being made in England by Wilfred Harris,<sup>9</sup> who in the early part of the following year reported successful injections of the Gasserian ganglion in 7 patients for the relief of trigeminal neuralgia. Harris's method appears to be quite like that employed by Taptas in his first two cases; and although the former published his results 2 months after the appearance of Taptas's paper, it is apparent that the two were working simultaneously and independently of each other, since Harris made his first injection 13 months before the appearance of his paper.

These earlier studies received an added stimulus from the elaborate investigations of Fritz Härtel, who in the following year published three papers (10, 11, 12) in which he described in the most minute detail an improved technique for injecting the ganglion and related his experience with a large number of patients treated by this method. Although the details of his technique were perhaps more accurate than those of any procedure hitherto described, the method was essentially that which had been previously recognized by Schlösser, Taptas, myself, and others, from experimental studies upon dissected preparations. With only slight variation, the skin puncture is made as though the second branch were to be injected, and the needle directed obliquely backward, upward, and inward toward the foramen ovale. Härtel, however, must undoubtedly be credited with having presented a description of the most accurate directions for subcutaneous approach to the Gasserian ganglion, the safest route, and the most extensive clinical experience which has yet appeared. Additional studies upon this subject have also been published under Härtel's<sup>13</sup> name, in the literature of 1914.

The advantages of his technique were soon recognized, and within the past 2 years Loevy,<sup>14</sup> Grinker,<sup>15</sup> and Maes<sup>16</sup> have each recorded a single instance in which Härtel's method has



been successfully employed in the treatment of trifacial neuralgia. One case is also reported by Kaufmann<sup>17</sup> in which he injected the ganglion according to Taptas's method, and C. D. Camp<sup>18</sup> has employed Harris's technique in 3 cases with satisfactory results. Sheldon of Kansas City, Mo., in an open letter, replying to Grinker, in the *Journal of the American Medical Association*, May 31, 1914, states that he has injected the ganglion by Ostwald's method 16 times in living subjects; but I have been unable to find any reference to a paper under Sheldon's name in which these cases are described.

During the interval between the appearance of Harris's paper, January 27, 1912 and that by Härtel, May 25, 1912, I repeated my earlier anatomical studies with the object of acquiring the necessary technique for making the ganglion injection. Before those studies were completed Härtel's paper appeared describing a method, some features of which were already known to me, and I set myself the task of improving upon the technique he had devised. The result of these experiments was the invention of an instrument which has enabled me to reach the foramen ovale with greater accuracy and safety, and reduced somewhat the degree of visualization necessary in making ganglion injections. The instrument (Fig. 1) and the method of using it were demonstrated before the Philadelphia Neurological Society, October 24, 1913,<sup>19</sup> and a full account of this technique will be given in a subsequent paper.

#### CLINICAL RESULTS FOLLOWING INTRAGANGLIONIC INJECTIONS OF ALCOHOL IN THE TREATMENT OF TRIGEMINAL NEURALGIA.

*Personal Use of the Method in 14 Cases.*—An opportunity to test the value of this treatment and the accuracy of my technique did not arise until March, 1913, at which time my first successful injection of the Gasserian ganglion was accomplished. Since then, I have performed the operation 13 times, upon as many individuals, for the relief of genuine neuralgia of the trigeminal nerve. In the most recent case, treated in September, 1914, the patient was entirely relieved when last heard from 2 months later.

My first patient, in whom the disease was bilateral, affecting the right second and third divisions and the left second division, received an injection into the right ganglion, and a deep injection for the left maxillary nerve. Although there has been a recurrence of pain in the maxillary division, for which she was again injected, I am informed in a recent letter (Nov. 13, 1914) that the right nerve has not troubled her since the original injection in March, 1913, and that she is entirely comfortable. A photograph of this patient, taken 2 days after treatment (Fig. 2), illustrates the distribution of anesthesia following the injection of the ganglion. In an effort to disguise the likeness, one of the most interesting features of the anesthetic boundary has been obscured. The upper limit involved a portion of the cornea, but only its lower half, and is represented by a line extending horizontally across the eyeball and passing through the center of the pupil. Above

this line, corneal sensibility was practically normal, except for an occasional point where sensation was slightly diminished.

The escape of the first division has an interesting explanation. Since this was my first attempt to inject the ganglion in a living subject, I had no desire to exercise any greater courage than the conditions demanded; and when I found the needle had been introduced to a sufficient depth to affect that portion of the ganglion from which the second division arises, I was more than willing to accept Harris's statement that the ganglion may be "fractionally" injected. Further experience has only convinced me of the truth of this statement and I have never attempted to affect the ophthalmic division when the disease is confined to the lower branches.

The dark spots within the anesthetic area represent the two skin punctures which were made before a successful injection was obtained. The site of the posterior one was first selected and is that suggested by Harris. Since this attempt was unsuccessful, I finally adopted my own technique in which the skin puncture is made at the point indicated by the anterior marking. The diffuse shading about the puncture wounds is due to slight erythema following the use of a freezing mixture before making the puncture.

In the second case (Fig. 3) the pain was confined almost entirely to the mandibular nerve, with an occasional twinge in the second branch, and I was quite willing to discontinue the injection when the appearance of disturbed sensation in the maxillary area assured me that, at least, a portion of the ganglion had been affected. Whether this disturbance in the second division was due to actual injection of the ganglion or to diffusion of the alcohol is difficult to determine; but in either event I feel that those cells from which the mandibular fibres arise were directly affected and perhaps permanently so.

An entirely successful injection of the ganglion is followed by all the symptoms characteristic of its complete removal, and in Fig. 4 the typical distribution of anesthesia is illustrated. Since the third branch alone was affected in this case, I decided to make simply a deep injection at the foramen ovale, but punctured the skin slightly lower than is customary according to the Taptas-Harris method for reaching the ganglion. I hoped by this means to make a successful injection of the mandibular nerve and perhaps affect that portion of the ganglion in which its cells were located. Much to my surprise, the needle entered the foramen with ease, and the resulting widespread anesthesia was obtained before the injection was completed. The operation was performed in August, 1913, and although a letter to the patient written in November, 1914, has not been answered, I feel confident that I would have been informed of a recurrence.

Of the remaining 11 patients, 3 had recurrences after 8, 10, and 12 months respectively, a development which I fully expected. Although at the time of injection there were undoubted evidences that at least a portion of the ganglion had been affected, I felt that the results were more likely due to infiltration rather than to actual injection of the ganglion. Immediately following the injection and for some time after there was complete anesthesia in the mandibular distribution,



but only partial anesthesia in the maxillary area, and a recurrence in the second division was predicted. One patient with carcinoma of the jaw which had invaded the cranial nerves of the middle fossa, producing intense pain in the trigeminal area, died from this primary disease 2 months after injection. Because of almost complete anesthesia of the face from the invading growth it was difficult to determine the effect of the injection by testing the cutaneous sensibility, and I could not see that there was any appreciable diminution in the pain. The 7 remaining patients have been entirely free from pain up to the present time, November 18, 1914. One of these cases is of especial interest and merits further consideration.

A man aged 43, was first seen by me in August, 1912, at which time he complained of pain in the right side of the face with twitching of the facial muscles upon this side. The original complaint, pain in the right upper jaw, began in 1905, and 4 years later the whole right side of the face became involved. At this time, 1909, an intracranial operation upon the ganglion was performed by a distinguished surgeon, but with practically no benefit; and the patient states that he had not more than left the hospital before he began to experience intense pain in the original distribution accompanied by marked twitching of the right facial muscles. The pain, however, was not of the same character as before the operation, but was described as a dull, deep-seated, continuous ache with intense exacerbations and was not induced by peripheral irritation. This condition had continued almost without interruption from the time of the operation—a period of more than three years—when he was referred to me with the request to inject Meckel's ganglion.

Examination at this time showed all the characteristic features indicative of the earlier operation, except that it was apparent that it had not been entirely successful. The motor function of the right trigeminal nerve was completely lost, but the sensory examination showed that the head and point of a pin could be differentiated throughout most of the trigeminal area, and warm and cool objects could be distinguished. Tactile sense was lost. Taste was preserved upon the right half of the tongue, and an acid solution invariably produced an exacerbation of the pain. There were constant spasms of the right face which occurred about every 15 seconds and were invariably associated with increase in the pain. At the height of the painful seizures it could be demonstrated objectively that all forms of cutaneous sensibility, except tactile impressions, were more acute.

It was my impression that a large part of his apparent suffering might be psychic, and various suggestive measures were tried, without appreciable benefit, before I consented to inject Meckel's ganglion. Without offering the patient or his physician the slightest hope of relief, I performed the injection in October, 1912, and although the patient imagined he derived some benefit, I could not see the least improvement from the operation. At any rate, he returned to me in April, 1914, stating that his suffering was such that he would end his life if not relieved.

During this interval I had acquired the technique for injecting the semilunar ganglion, and believing that his suffering might be explained by incomplete removal of the Gasserian ganglion, I suggested an injection of alcohol into the ganglionic fossa; and as an alternative, injection of the facial nerve at the stylo-mastoid foramen with the hope of relieving the facial spasm. Without much confidence in either procedure, I determined to attempt the ganglion injection. Accordingly, April 28, 1914, by employing the technique I had devised, I was fortunate enough to place the alcohol in the desired location. To my astonishment, the facial spasm immediately ceased, the pain was relieved, and all forms of cutaneous sensibility throughout the right trigeminal area were completely abolished. At my request, the patient called to see me November 10, 1914. At this time he was still entirely comfortable and objectively the condition was the same as immediately after the injection.

The duration of relief in the 14 cases may be summarized, as follows: At the present writing, November 18, 1914, a little more than 18 months have elapsed since my earliest injection. During this period, 6 patients were treated more than a year ago and are still free of pain—the longest period being 18 months. Four patients, treated within the last 12 months of this period, have had no return. The 3 patients in whom only partial injections were obtained, returned for further treatment. The one death from carcinoma has already been referred to.

*Immediate and Remote Effect from Ganglion Injection.*—During the introduction of the needle little or no pain is felt until the foramen ovale is reached, when a sharp neuralgic attack may be experienced in some portion of the mandibular nerve. It has been the practice of some to inject at this point a few drops of novocain solution, but I have not yet found this necessary, and usually instil a few drops of alcohol at once, which lessens somewhat the pain usually induced by entering the foramen. After the needle has entered the foramen, pain is felt in the maxillary or supraorbital area, depending upon the depth to which it has been introduced; and it has been my practice to inject a few drops of alcohol with each successive step. Strangely enough, the pain associated with injection of the ganglion, although of wider distribution, is not greater than that experienced in making the deep neural injection; and occasionally I have performed the operation, when the pain was so slight, that I had some doubt concerning the accuracy of my technique until the characteristic sensory disturbances appeared.

After a successful injection, the characteristic disturbances following surgical removal of the ganglion are observed throughout the motor and sensory distribution of the trigeminal nerve; and taste is lost upon the anterior portion of half the tongue. The conjunctival, corneal, and sneezing reflexes are abolished, and various subjective feelings of swelling, fullness, numbness, and tingling are complained of. Headache of a few hours' duration may be an unpleasant consequence in some cases; and I have occasionally observed the restlessness, change in pulse rate, and vomiting described by Pussep, but am



inclined to regard them as a mild form of shock. I have not seen them in cases in which the nervous system was under good control.

The duration and character of the sensory disturbances following injection are variable. As a rule, the loss of sensibility is not so complete or quite so extensive as that following removal of the ganglion. A patient, who immediately after the injection shows complete physiological destruction of the ganglion, may within the next 24 hours show marked shrinkage in the anesthetic area; so that what seems to be complete destruction of the ganglion, later may turn out to be only partial. The shrinkage of the anesthetic area may involve all three divisions, so that the entire field is smaller than immediately after the injection; or the return of sensation may be confined to one branch alone—usually the ophthalmic. The most persistent anesthesia is usually found within the mandibular area; although it is occasionally observed that the original widespread anesthesia persists. It seems that not all forms of sensibility are equally affected, since it has been my usual experience to find that, with returning sensation, the ability to differentiate the head and point of a pin is the last to be recovered; and it is not infrequently lost for many months after tactile sense has returned. The motor function is almost invariably recovered after 6 or 8 months, and taste is regained after a much shorter period.

*Complications.*—It has been my good fortune not to encounter any serious unpleasant results from either the deep neural or ganglionic injections. The most annoying one to the patient that I have observed has been the development of an occasional hematoma. Other complications, such as paralysis of the oculomotor nerve, the facial nerve, or the soft palate, and dilatation of the pupil, have been described. They were, however, of short duration and were thought to be due to diffusion of alcohol into the cavernous sinus, or perhaps along the base of the pons. Härtel has observed herpes facialis in four instances, keratitis three times, corneal ulcer once, and paralysis of the sixth nerve in one case. In some instances, loss of consciousness and collapse, of a few minutes' duration, vertigo, nystagmus, and nerve deafness have been observed. Simons, in studying Härtel's series of cases from Bier's clinic noted the symptoms of meningismus in one instance. The occurrence of these complications has usually been explained by diffusion of alcohol into the subdural space, and I shall refer to this feature again in my experimental studies. One death has been recorded in Härtel's series, but it seems that this was not due to the injection of alcohol, and is accounted for by the introduction of an incompletely sterilized solution of novocain and the subsequent development of septic meningitis which was confirmed at autopsy. Such complications as may arise from injury to important anatomical structures during the introduction of the needle belong properly to a discussion of technique and will not be considered at the present writing.

*Selection of Cases for Ganglionic Injection.*—The choice between injection of the ganglion and deep neural injection will depend somewhat upon the severity of the attack, the con-

stitutional peculiarities of the patient, and the number and arrangement in which the several trigeminal divisions are affected. If the attacks are so severe that immediate relief is urgent, and the patient is unwilling to accept the prospect of failure at any single attempt to reach the ganglion, greater assurance of success, at any one sitting, will be offered by the deep neural injection.

The distribution of the pain, either in a single branch or in any of the several possible combinations of the three divisions, is an important feature. If the attacks are confined to the first or second branch alone or combined, it would be more conservative to resort to a deep injection for the second division and a superficial injection at the supraorbital foramen. The element of uncertainty in entering the foramen ovale and the necessary damage to the third division in making the attempt are sufficient reasons for adopting the less radical measures.

When the third division is involved, either alone or in conjunction with the maxillary division, choice of the method of injection will depend somewhat upon the skill one has acquired in making ganglionic injections and the exigencies of the individual case. While no harm can be done in trying to reach the ganglion, the patient's suffering may be so intense that immediate relief is desirable; and it would be more promising to make the deep injection for the individual branches than to attempt the ganglionic injection. At the same time it is probable that, even in a deep injection for the third branch, the ganglion may be reached if the skin puncture is made according to Harris's method. For this reason, if both the second and third divisions are affected, the mandibular branch should be injected first.

Obviously, in every case where all three branches are involved, injection of the ganglion may unhesitatingly be attempted. Should repeated efforts be unsuccessful, deep injections for the second and third divisions, and a superficial injection of the first division may be performed. If these fail to give relief, ganglionectomy is still left as a last resort.

The advanced age of the patient is no contraindication to either deep neural or ganglionic injections; and I have upon one occasion administered this form of treatment without harmful effects to a patient 79 years of age, who had, at the time, hypertrophic cirrhosis of the liver, interstitial nephritis, aortic and mitral insufficiency, and hypertrophy of the heart.

From clinical experience alone, it would be difficult to make a positive statement concerning the permanency of results obtained from injection of the ganglion. Assuming that Taptas's earliest patient, treated some time in 1911, has had no recurrence up to the present time—a period of little more than 3 years—the interval has been too short for the deduction of trustworthy conclusions. Deep neural injections have been known to give relief for a similar period. It is extremely desirable, however, that more accurate knowledge concerning this phase of the subject be acquired as early as present methods of investigations will permit, and I felt that additional information might be obtained from:



EXPERIMENTAL INJECTION OF THE GASSERIAN GANGLION  
IN LOWER ANIMALS.

It is surprising how little attention has been given to the laboratory study of this subject. The first experimental investigations of this character were, as far as I am aware, made by Brissaud and Sicard<sup>20</sup> in 1907. While their paper is concerned almost entirely with deep neural injections, they suggest that more lasting results should be obtained by injecting the ganglion directly, and refer very briefly to their single experiment of this character upon the dog. The method by which the ganglion was approached and the percentage and amount of alcohol injected were not recorded. Four weeks after the operation, the ganglion and its several divisions were studied microscopically and it was found that the nerve fibres showed "complete degeneration and fragmentation" and there was "almost total disappearance of the ganglion cells." The paper is not illustrated.

The only other researches of this character were made by Otto May,<sup>21</sup> in 1912. May's studies were more extensive and included an investigation of the effect produced when alcohol is injected into: (1) Purely sensory nerves; (2) mixed nerves, and (3) the Gasserian ganglion. The last group, alone, is of particular interest at the present time. The experiments were made upon 3 cats and 1 goat, and in each instance the ganglion was exposed by the subtemporal route and injected with 0.75 cc. of 80 per cent alcohol in two of the animals, and with a similar amount of absolute alcohol in the two remaining experiments.

The animals were sacrificed and the ganglia removed for microscopic study 7, 16, and 18 days after injection. The nerve cells in the ganglia of the cat were only slightly altered. Some showed moderate chromatolysis and were stained more deeply than ordinarily; but in general, the "ganglion cells were quite normal looking." Degenerative changes in both the intraganglionic and extraganglionic fibres were variable. Within the ganglion the fibres near the origin of the several branches were most markedly affected, while those of the nerve trunks showed, in some instances, almost complete degeneration in one branch, with little or no alteration in others. In one instance the spinal tract of the fifth nerve was degenerated and the mesencephalic root was affected. In the goat, marked neuroparalytic keratitis developed and the animal was sacrificed. The injected ganglion was swollen and adherent, and sections showed a fair number of profoundly altered cells, although the majority were quite normal. Of the three branches, the first was about one-half degenerated, the second showed only a few altered fibres, and the third was practically normal. The proximal root contained about one-half the number of fibres usually present, and the spinal tract showed marked degeneration in its lower part, which became less pronounced as the nucleus was approached. It did not appear that absolute alcohol is any more destructive than the weaker solution, and May concludes that it is impossible to produce complete destruction of the Gasserian ganglion by a single injection of alcohol.

I could not find a record of other experimental studies upon this subject; and since May's investigations left undetermined several questions about which I had some concern, it appeared worth while to repeat his experiments but under conditions more nearly like those existing in the clinical use of ganglionic injections. Obviously subcutaneous injection of the ganglion in lower animals offers too many difficulties to be of experimental value and the nearest approach to such a method, by exposure of the foramen ovale, was employed upon 4 dogs, 2 small terriers, a full-grown hound, and a large bulldog.

In each experiment the following technique was adopted: Under general anesthesia, the right Gasserian ganglion was injected with 2 cc. of 85 per cent alcohol by exposure of the foramen ovale, through which a curved, graduated needle was introduced into the ganglionic fossa. The injection of alcohol was begun as soon as the needle entered the foramen and continued at successive steps until a depth of 2 cm. had been reached, a distance more than sufficient to include the entire ganglion. During the operative approach to the foramen ovale care was taken to avoid injury to the fibres of the facial nerve and of the third trigeminal division. Daily, post-operative clinical observations were made in each case for a period of 10 days, when the animal was asphyxiated and both Gasserian ganglia were removed for further study.

Care was taken in removing the ganglion to obtain enough of the root and the three nerve trunks for separate study. After fixing in 10 per cent formalin and hardening in Müller's fluid the specimens were imbedded in celloidin and sectioned as follows: The entire ganglion was cut longitudinally so as to include portions of each division and root. All sections were retained, but not kept in series, and more than one hundred from the upper and lower surface and the center of each ganglion stained and examined. The three branches and the root were cut in cross-sections and stained by the usual method. The uninjected specimens were used merely for control, and sections were made of the ganglion only.

Several sections from each block of tissue were stained by the following technique: Hæmalum and acid fuchsin, Weigert's myelin stain, Marchi osmic acid; and in addition to these thionin preparations were made from each ganglion.

Dogs Nos. 1 and 2. Small terriers. Exposure of the foramen ovale in the dog is, at best, a difficult operation, so that, in the first two experiments upon the smaller animals, I could not feel quite certain that the needle had entered the foramen and the results were more or less unsatisfactory. Upon recovery from the anesthetic one of the animals showed slight disturbance of sensation in the trigeminal area, and some haziness of the cornea with diminished sensibility. These symptoms were, however, of short duration, and had completely disappeared by the fifth day. Histological preparations from these two ganglia showed little or no alteration, except that in the one removed from the dog in which the transitory sensory changes developed, there was slight fragmentation of the myelin within the mandibular division. This, no doubt, could have been due to trauma in searching for the foramen or to infiltration of alcohol about the nerve trunk.



Dog No. 3. Large, yellow hound. In this and the following experiment, the larger size of the animals made the exposure of the foramen much less difficult; so that there was no question about the location of the needle, and the clinical and histological observations were so decided that I shall describe them more in detail.

*Clinical Observations.*—After recovery from the anesthetic the animal did not respond to the usual forms of cutaneous irritation in any part of the right trigeminal distribution and the right cornea was insensitive. The following day the cornea was still insensitive and slightly hazy, but the loss of cutaneous sensibility not so complete as immediately after recovery, although there was marked hypoaesthesia throughout. After being repeatedly pricked with a pin the animal would at times make indifferent efforts to withdraw the head. The condition remained unchanged up to the tenth day, when the ganglia were removed.

*Necropsy.*—Nothing abnormal was noticed upon removal of the calvarium, and the brain showed no gross changes upon its surface or at the base. There were no evidences of trauma or inflammation about the ganglia. Upon removal, however, it was apparent that the right ganglion was swollen and edematous, and by actual measurement, 1.5 mm. larger in its transverse axis than the uninjected specimen. This difference is clearly visible in the photographs of the two ganglia in which the exposures were made at the same focal distance (Figs. 5 and 6).

*Microscopic Examination.*—Each of the three branches showed a moderately extensive degeneration of the myelin in both the Weigert and Marchi preparations; and the hæmalum acid fuchsin specimens showed a good proportion of swollen, irregular, faintly staining axis cylinders in all three divisions. Similar changes were observed in the root, though not quite so extensive. Very slight changes were found in the ganglion by any of the methods of staining. In every section, however, a few cells could be found in which there were evidences of beginning disintegration, such as: swelling, chromatolysis, displacement of the nucleus, and increased pigmentation. There were no evidences of an inflammatory reaction other than a moderate proliferation of the pericellular nuclei.

Dog No. 4. Large bulldog. In this experiment the technique was altered slightly in hopes that I might obtain more definite information concerning a question Harris<sup>5</sup> had called attention to in one of his earlier papers, and about which I had had some anxiety in making ganglionic injections.

In writing of deep, neural injections for the third branch Harris states that care should be exercised lest the needle enter the foramen ovale and pass through it into the subdural space. Yet, in a later paper<sup>9</sup> upon injections of the ganglion he takes advantage of this supposedly hazardous procedure to determine the accuracy of his technique, by introducing the needle until cerebral fluid drops from its free end. Being assured, by this means that the foramen has been entered, he withdraws the needle slightly, until fluid ceases to flow, and commences the injection. It is gratifying to learn from a recent paper by Harris<sup>22</sup> that he has since discontinued this practice.

I adopted this means of orientation in the case of the bulldog, and instead of withdrawing the needle, injected 1 cc. of 85 per cent alcohol directly into the subdural space. The needle was then gradually withdrawn and the ganglion injected. Neither during or following the intradural injection were there any evidences of untoward symptoms. The pulse and respiration were unaffected and there were no evidences of cranial nerve involvement other than those to be described in the trigeminal area. While, in this particular instance, the dog survived the test without complicating conditions, I cannot see the necessity or wisdom of subjecting human beings to a similar test. Nevertheless, this knowledge, if of any value, may be somewhat reassuring to those who accidentally enter the dural space.

*Clinical Observations.*—The post-operative notes are practically the same as in the preceding case, except that evidences of destruction of the fifth nerve were more pronounced. There was complete anesthesia throughout its distribution and the cornea rapidly became cloudy and later showed ulceration. These symptoms persisted without change until the animal was asphyxiated.

*Necropsy.*—Ten days after operation the dog was sacrificed and the brain injected *in situ* with 10 per cent formalin and removed. No gross changes were observed upon its convexity, but at the base there was a small puncture wound within the right pyramid just below the inferior border of the pons, which had been produced by the introduction of the needle through the dura in my search for cerebral fluid. The puncture was quite superficial and did not cause any obvious clinical symptoms. No gross changes were found in the ganglia except the swelling and edema in the injected specimen (Figs. 7 and 8). The greatest transverse measurement of the two ganglia showed a difference of 2 mm.—the left measuring 7 mm. and the right 9 mm. As in the previous experiment, the ganglia were photographed at the same focal distance.

*Microscopic Examination.*—The histological changes in the ganglion and its peripheral divisions are pronounced.

*Ophthalmic Nerve, Cross-Section.*—The hæmalum acid fuchsin section shows a large number of greatly swollen, distorted, faintly staining axis cylinders; and it requires considerable search to find any that appear to be normal. There are no indications of an inflammatory reaction. In the Marchi preparation there are scattered droplets of myelin throughout the section; but the stain is, in general, unsatisfactory. The Weigert myelin stain (Fig. 9) shows almost an entire absence of nerve fibres. The few remaining fibres, seen in the illustration, take the stain poorly and show evidences of fragmentation.

*Maxillary Nerve, Cross-Section.*—Changes similar to those observed in the first division are found in sections stained by each of the above methods, although the destruction of fibres, is not so complete or so extensive. In the Weigert preparation (Fig. 10) it is observed that considerably more than one-half the section is devoid of fibres and that the remaining ones are irregularly scattered and faintly staining. Many of the larger black droplets are in reality myelin fragments.





FIG. 1.—Instrument devised by the author for locating the foramen ovale.

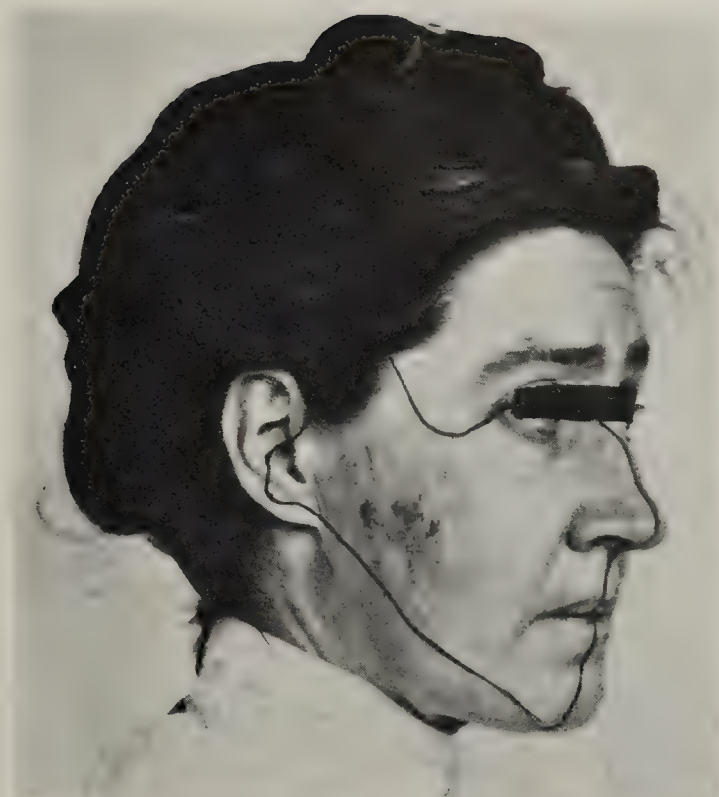


FIG. 2.—Photograph of a patient showing outlines of anesthesia after incomplete injection of the Gasserian ganglion. Attacks confined to second and third divisions.



FIG. 3.—Photograph of a patient showing a more limited area of anesthesia after injection of the Gasserian ganglion. No involvement of the cornea.



FIG. 4.—Photograph of a patient showing anesthesia throughout the entire trigeminal area after complete injection of the Gasserian ganglion. The white patch in front of the ear represents a cotton-collodion dressing over the skin puncture.









FIG. 5.—Uninjected left Gasserian ganglion. Dog No. 3. Hound. Greatest transverse measurement, 5 mm.



FIG. 6.—Injected right Gasserian ganglion. Dog No. 3. Hound. Showing swollen condition as compared with the left ganglion. Greatest transverse measurement, 6.5 mm.

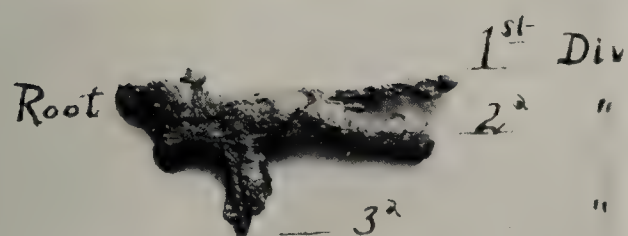


FIG. 7.—Uninjected left Gasserian ganglion. Dog No. 4. Bulldog. Greatest transverse measurement, 7 mm.

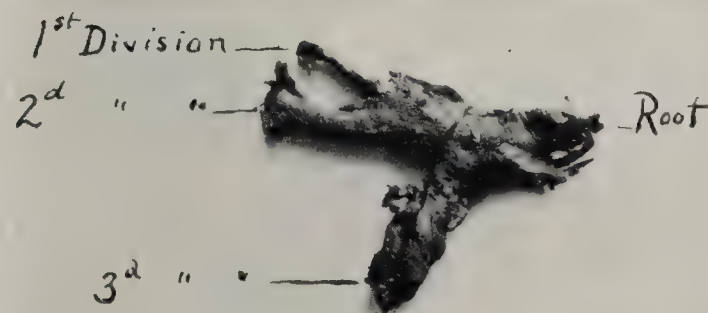


FIG. 8.—Injected right Gasserian ganglion. Dog No. 4. Bulldog. Showing swollen condition as compared with the left ganglion. Greatest transverse measurement, 9 mm.

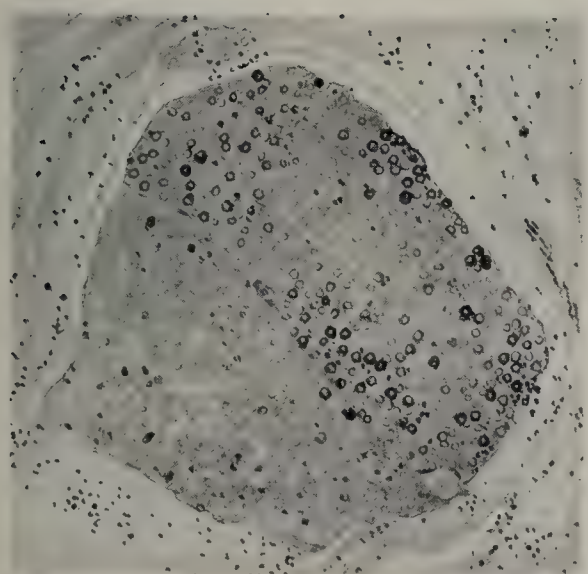


FIG. 9.—Dog No. 4. Cross-section, ophthalmic division, right trigeminal nerve, ten days after injection of the ganglion with alcohol. Weigert myelin stain.

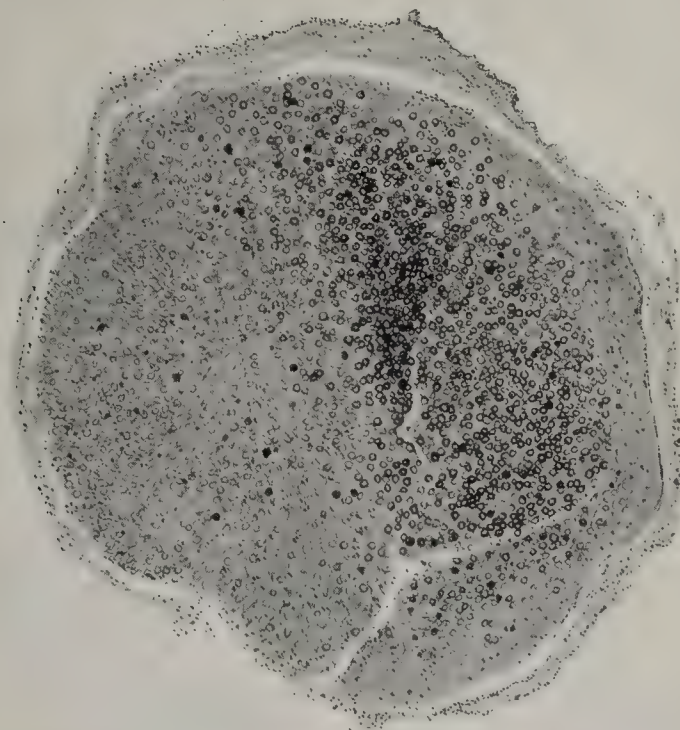


FIG. 10.—Dog No. 4. Cross-section, maxillary division, right trigeminal nerve, ten days after injection of the ganglion with alcohol. Weigert myelin stain. Many of the remaining fibres show fragmentation.







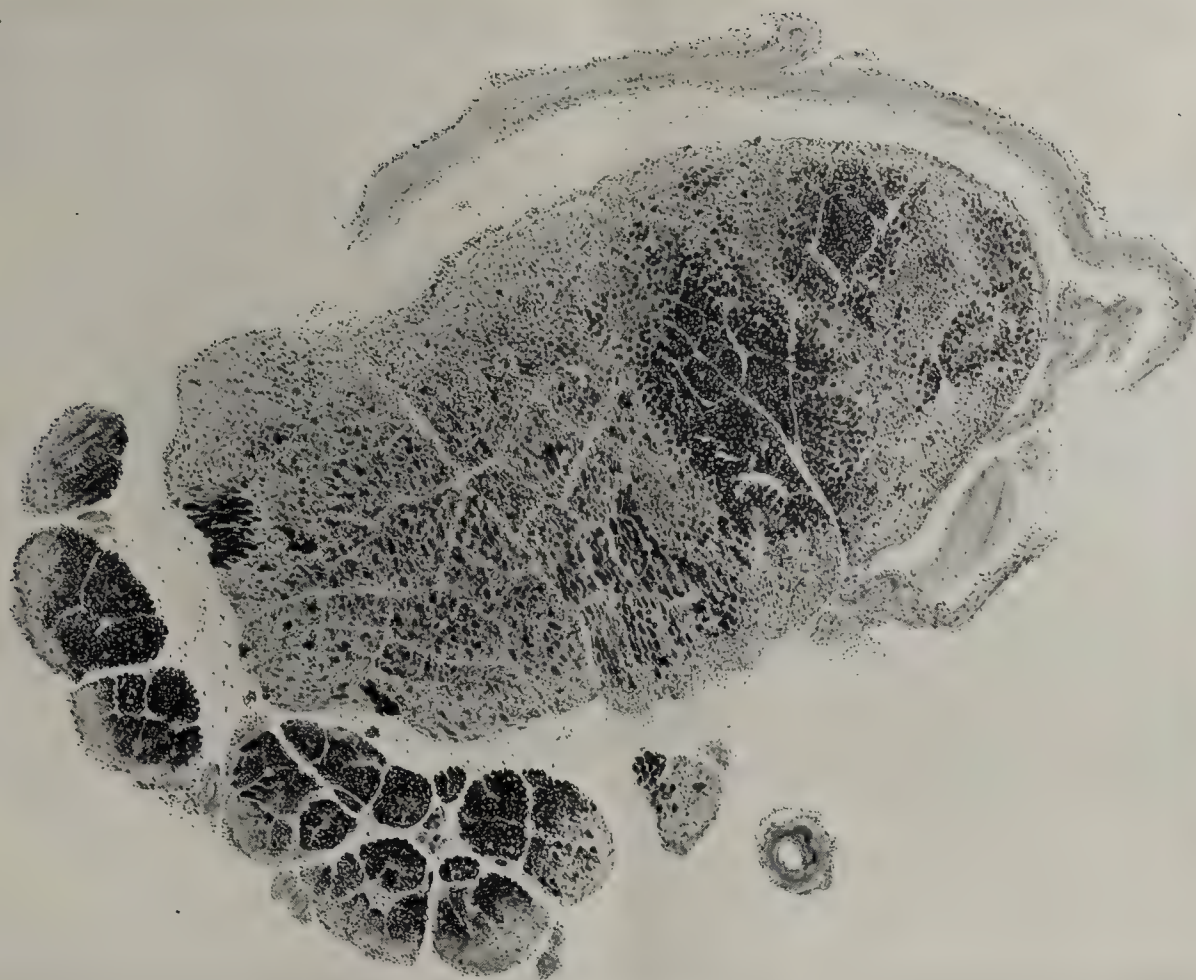


FIG. 12.—Dog No. 4. Cross-section, sensory and motor roots, right Gasserian ganglion ten days after injection with alcohol. Weigert myelin stain. Observe slight destruction of motor root as compared with that in the preceding figure.

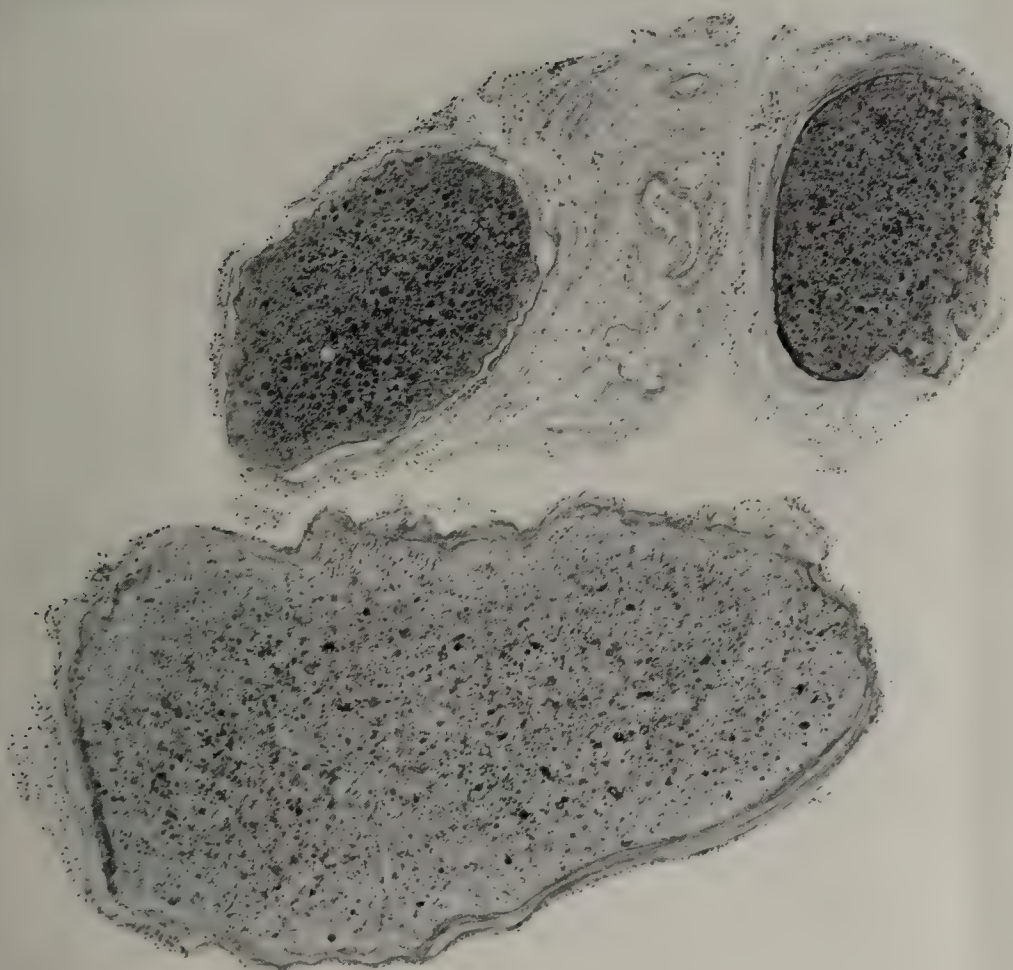


FIG. 11.—Dog No. 4. Cross-section, mandibular division, right trigeminal nerve, ten days after injection of the ganglion with alcohol. Weigert myelin stain. Complete degeneration of both motor and sensory fibres.

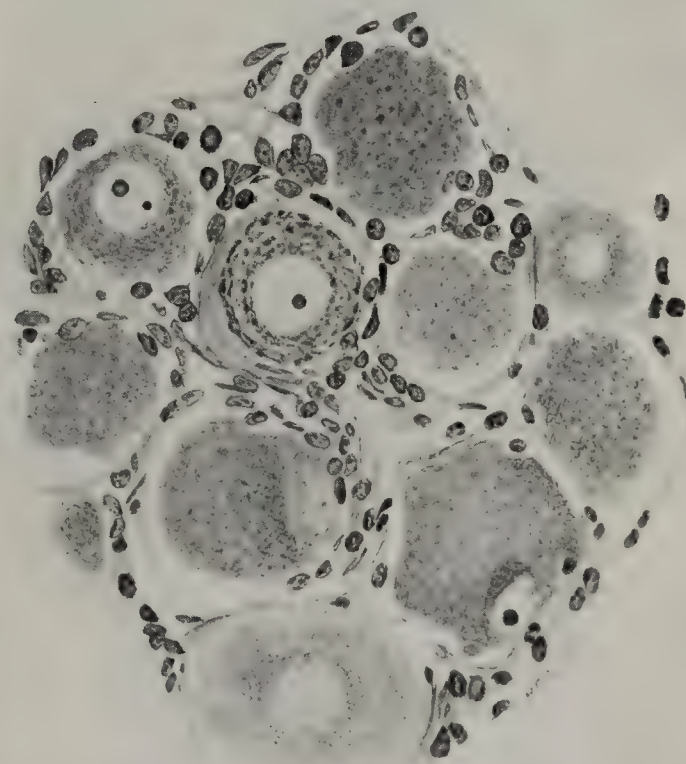


FIG. 13.—Dog No. 4. Section of right Gasserian ganglion ten days after injection with alcohol. Thionin stain. The proportion of normal and diseased cells is fairly accurately represented.







*Mandibular Nerve, Cross-Section.*—As might be expected, the third division shows the most extensive and complete degeneration. Practically no healthy axiscylinders are found in the hæmalum acid fuchsin preparation, and there is a moderate inflammatory reaction in parts of the section. The Marchi preparation does not give a clearly defined picture, although the section contains many very fine black droplets. Both the motor and sensory portions show complete disintegration of the myelin in the Weigert staining (Fig. 11).

*Ganglionic Root, Cross-Section.*—Degenerative changes are found in both the motor and sensory portions by all methods of staining. The Weigert section (Fig. 12) shows complete disintegration of myelin in places, and extensive fragmentation; but there are quite a number of healthy fibres remaining. The small motor portion has been affected, apparently in a lesser degree. This preponderance of normal fibres in the motor root is rather significant and may be explained by the fact that the greatest degeneration in that division must be peripheral to the point of injection; and since the nerve cells from which these fibres arise were not affected, it is to be expected that the number of normal fibres will increase as the motor nucleus is approached. By comparing this illustration with the preceding one it is observed that in the maxillary nerve the motor fibres are completely degenerated. This difference in the appearance of the two sections will be understood when it is recalled that the section through the ganglionic root is much nearer the nucleus of origin of the motor fibres, and that the injection probably did not occur much beyond the posterior border of the ganglion.

*Right Gasserian Ganglion.*—Apparently the entire ganglion has been affected. Throughout all sections, distinct and widespread changes are present. Moderate inflammatory changes are observed in the hæmalum acid fuchsin preparation, and the intraganglionic fibres are swollen and fragmented. Disintegration of the myelin is pronounced in the Weigert section. The thionin stain (Fig. 13) shows marked alteration in the nerve cells throughout the ganglion. Many cells are swollen and irregular, and show complete disintegration of the tigroid substance, and eccentric nuclei. In places, the cell chamber is filled with disintegrating fragments and there is general proliferation of the capsular cells. Quite a few nerve cells show those border-line changes between disintegration and repair which create some doubt as to the final result, although, I believe a considerable proportion will ultimately recover.

*Medulla.*—The spinal tract of the fifth nerve shows slight degeneration in the Weigert preparations; and there is a small area of degeneration in the right pyramid corresponding to the punctured wound inflicted during the injection.

I cannot close this description of the experimental studies without a word of gratitude to Dr. William S. Halsted for his generosity which gave me the privileges of the Hunterian Laboratory, and to his Assistant, Dr. J. A. Hunnicutt, for his valuable services in the more complicated surgical technique. I am also indebted to Dr. Franklin P. Mall for the use of the Anatomical Laboratory, in which the histological studies were conducted.

## CONCLUSIONS.

1. In the treatment of trigeminal neuralgia, a single successful injection of alcohol into the Gasserian ganglion is followed by immediate relief of pain and all the symptoms indicative of its complete physiological destruction.

2. Although a general anesthetic is not administered, the painfulness of the injection is not unbearable or greater than that experienced in making deep intraneural injections.

3. In experienced hands, this form of treatment is without serious risk, and no fatalities have been recorded as a direct result of the injection.

4. In spite of the contentions of Alexander and Unger, injections in man by exposure of the ganglion appear to be unwarranted and lacking in judgment, except in rare cases in which this slight saving of time may determine the immediate result during exposure of the ganglion. It is conceivable that in performing the subtemporal operation for removal of the ganglion, emergencies might arise which would demand prompt closure of the incision, or prevent further approach to the ganglion. Under these conditions, if the ganglion is in view or accessible, direct injection might be practised; otherwise the original operation for removal or avulsion of the root should be employed.

5. If deep neural injections have been unsuccessful, and repeated attempts to inject the ganglion by the subcutaneous method have failed, an effort might be made to inject through the exposed foramen ovale before resorting to the subtemporal operation for removal.

6. It has been demonstrated, by fractional injection, that the extent of destruction may be, in a measure, limited to that portion of the ganglion from which the affected nerve trunk originates; and that not infrequently the corneal fibres can be spared.

7. From the distribution of corneal anesthesia, following partial injections of the Gasserian ganglion, it appears that the upper and lower halves of the cornea receive separate innervation.

8. In cases of bilateral trigeminal neuralgia, injection of the ganglion possesses distinct advantages over other methods of radical treatment. Since anatomical continuity is not actually destroyed and the motor nucleus is not directly affected, conditions are most favorable for recovery of motor function; while sensation should be permanently lost if the ganglion is completely destroyed. Thus, by allowing sufficient time for regeneration in the motor root bilateral ganglionolysis might be safely practiced.

9. Clinical observations have been too recent to furnish reliable information as to the permanency of relief after ganglionic injections; and experimental studies appear to indicate that it is not probable that the ganglion can be completely destroyed by a single injection of alcohol. It is my opinion, however, that by repeated injections of the ganglion its complete destruction may finally be accomplished.

10. Finally, it is a pleasure to make this public acknowledgment of my indebtedness to many of my colleagues who have referred patients to me for treatment by this method; and to



Dr. H. M. Thomas for the unrestricted privileges he has given me in the use of material from his clinic. I am also deeply indebted to Dr. Harvey Cushing, from whom I received my earliest instruction in the technique of deep neural injections.

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## ANIMAL CALORIMETRY.\*

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A respiration calorimeter is an apparatus designed for the measurement of the gaseous exchange between a living organism and the atmosphere which surrounds it and the simultaneous measurement of the quantity of heat produced by that organism.

An Atwater-Rosa-Benedict calorimeter suitable for work with dogs and babies was first constructed five years ago by H. B. Williams for the use of the physiological laboratory of the Cornell University Medical College. The problem of measuring 7 calories of heat produced in an hour by a baby weighing 3 kilograms was different from that presented by the measurement of 70 calories produced by an adult. This led to the addition of certain technical refinements to the calorimeter. The small calorimeter has been successfully used with dogs and babies. For the first time direct and indirect calorimetry were found to agree during hourly periods of experimentation.

The satisfactory working of this apparatus led the writer to seek and obtain a grant from the Russell Sage Institute of

Pathology, in order that a respiration calorimeter might be constructed and maintained in Bellevue Hospital. As an indication of the perfection of this latter instrument, Du Bois reports that the actual measurement of heat in all the experiments on normal controls agrees within 0.17 per cent with that calculated from the oxygen absorption.

The respiration calorimeter consists of two functional parts, one for measuring the gas exchange and the other for determining the heat production of the subject. The apparatus is a constant temperature, water-cooled calorimeter. That is to say, the walls of the box are maintained at a constant temperature, while the heat lost by radiation and conduction from the subject is carried away by a stream of running water whose volume multiplied by the increase in its temperature measures the calories absorbed.

The experimental procedure which has become conventional in the laboratory is to give a standard maintenance diet to a dog at five o'clock the evening before the experiment and then to determine the *basal metabolism* the next day beginning about eighteen hours after food ingestion. Having determined this level of heat production the material to be tested is given on another day eighteen hours after the regular food ingestion

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and the increase in metabolism is noted. A similar program is used to determine the basal metabolism in man.

It has been found that after giving 50 grams of glucose to a dog the heat production may rise 30 per cent above the basal requirement. After giving 200 grams of glucose to a man, whose basal metabolism was fourfold that of the dog, the heat production was only increased 12 per cent. Therefore, after giving quantities of glucose which bear the same relation to the total metabolism, the effect is far greater in the dog than in man. The administration of fructose or sucrose causes a somewhat greater increase in metabolism than does glucose. The power of the dog to oxidize galactose is much less than that for the other sugars named, and there was no power whatever to oxidize milk-sugar, probably on account of the absence of lactase from the intestine. Some people who cannot digest milk may suffer from the absence of this enzyme.

Grafe has found that the metabolism of a dog rose 33 per cent above the fasting level during a day on which carbohydrate to an extent of three-and-a-half times the energy requirement was given. Grafe states that the continued administration of carbohydrates gradually raises the power of the organism to oxidize them. There is, however, nothing in substantiation of this theory. The power of the organism to oxidize carbohydrate depends largely upon the influx of material into the blood stream. When this influx ceases and the excess of carbohydrate is laid down as inert glycogen the usual basal metabolism returns.

Benedict suggests that the high metabolism after carbohydrate ingestion is due to acid stimulation. He cites an experiment in which glucose administered to a diabetic caused no increase in metabolism, whereas fructose caused an increase even though it was completely converted into glucose and eliminated as such. It should be noted that the transformation of fructose into glucose is believed to be through methyl-glyoxyl, and not through acid bodies. Repetition of these experiments, using dogs made diabetic with phlorhizin, failed to produce an increase in metabolism after giving either glucose or fructose. That a stimulus to metabolism such as might be given by lactic acid is absent, when sugar is metabolized, is indicated by the fact that when alanin, which is convertible into lactic acid in the organism, is administered with glucose a far more powerful effect upon metabolism is obtained than when a comparable quantity of glucose is given alone.

Furthermore, if acid were produced in any quantity, carbon dioxide would be driven from the blood and tissues. This point was studied by A. L. Meyer, who found that the ingestion of 50 grams of glucose by a dog was without effect upon the carbon dioxide content of the blood. Since the carbon dioxide content is a most delicate index of the hydrogen ion concentration of the blood, it would appear that the increase in metabolism after glucose ingestion is not due to acid stimulation in the sense of Benedict's theory. It seems better to describe the increased metabolism as the metabolism of plethora. A larger number of glucose molecules are present and these in increased number undergo metabolism into methyl-glyoxyl radicles available for cell nutrition. Perhaps the superior

power of fructose to increase metabolism lies in the fact that fructose must be split into readily oxidizable molecules of methyl-glyoxyl before it can be transformed into glucose and glycogen; whereas, glucose may immediately be withdrawn from the circulation and laid down as glycogen.

On the basis of these facts there seems no reason to discard the idea of a metabolism of plethora, that is, one in which the mass action of readily oxidizable molecules may increase metabolism.

A further reason for this belief was found in the behavior of alcohol. When 50 grams of glucose were given the heat production was increased 30 per cent, and after 70 grams it increased 35 per cent. When 9.4 grams of absolute alcohol were given the increase was 15 per cent; whereas, when 50 grams of glucose plus 9.4 grams of alcohol, together containing the same number of calories as 70 grams of glucose, were administered, the heat production rose 43 per cent. From this it may be concluded that the resultant effect of the ingestion of glucose and ethyl alcohol is the sum of the effects which each would have produced alone. Alcohol in combustion yields a respiratory quotient of 0.67. The result of the ingestion of alcohol with glucose was to greatly lower the respiratory quotients usually obtained after glucose ingestion. It is evident, therefore, that the small molecules of alcohol containing two atoms of carbon are readily oxidized when given with sugar, and raise the heat production to a greater height than does glucose when given alone.

The effect of protein in increasing metabolism is very powerful. Rubner found that the heat production of a quietly resting dog could be nearly doubled by the ingestion of protein. The study of protein metabolism has lately become the study of the fate of the 17 amino-acids of which protein may be composed. It has been shown in phlorhizin glycosuria that alanin and glycocoll are completely, and that aspartic and glutamic acid are largely, converted into glucose and eliminated in the urine. To this list Dakin has added serin, cystin, ornithin, prolin and arginin. Thus 9 out of 17 amino-acids are known to be convertible wholly or in part into glucose.

It has been found, when meat in large quantity is given to a dog, that although the protein nitrogen appears freely in the urine protein carbon is retained in the organism. Determinations with the respiration calorimeter during this period show that the respiratory quotient corresponds exactly with what one would expect if glycogen were being retained, and the calculation of indirect calorimetry on the same basis of glycogen retention shows agreement with the heat production as actually found. If the retained carbon be calculated as fat there is a discrepancy of 10 per cent between indirect and direct calorimetry. There is, therefore, no doubt that sugar formation is a function of the normal organism.

Rubner's theory of the rise in metabolism after meat ingestion was that all those fragments of protein metabolism which were not converted into sugar were oxidized as so much valueless material. This theory fell with the demonstration that glutamic acid, which is in part converted into glucose and in part into oxidizable radicles, does not cause any increase in



metabolism; whereas, glycocoll and alanin, which are completely convertible into glucose, exercise a powerful influence. Recent experiments have shown that the hours immediately following the administration of glycocoll are the hours of its greatest metabolism and these are coincident with the hours of the greatest heat production. It has furthermore been found that the extra heat production after giving glycocoll may nearly or quite equal the entire energy content of the glycocoll itself.

The results of glycocoll ingestion also resemble those of protein ingestion in that the rise in metabolism is directly proportional to the amount of substance given.

Although glycocoll is convertible into glucose it does not act like glucose. Thus, when 50 grams of glucose plus 20 grams of glycocoll, which together would produce 66 grams of glucose in the organism, are given to a dog, the heat production is nearly twice as great as 70 grams of glucose given alone would produce. The stimulus to heat production following the ingestion of glycocoll must, therefore, be of an entirely different character from that effected by an equivalent amount of glucose.

The behavior of alanin follows these same laws.

Are glycocoll and alanin merely oxidized as so much waste or do they stimulate metabolism? The answer is to be found in experiments on phlorhizinized dogs. Here glycocoll and alanin are not oxidized. They are eliminated unoxidized in the urine in the form of sugar and urea and yet the heat production is largely increased. The respiratory quotients found correspond with the respective theoretical requirements after the ingestion of these substances.

The specific dynamic action of protein as defined by Rubner has now been narrowed down to a question of chemical stimulation of the cell. Is the stimulus due to the glycocoll and alanin or to the glycollic acid or lactic acid formed from them? Rubner has found that when protein was retained in the organism it exerted no specific dynamic action. Recent calorimeter experiments of Hoobler with babies fed on *Eiweissmilch* also show that when protein is retained there is no increase in

metabolism. It seems therefore demonstrated that the stimulus to higher metabolism is derived from certain keto- or oxy-acids of the types of pyruvic or lactic acid liberated during protein metabolism.

Benedict has advanced the theory that the increased metabolism in diabetes is due to acidosis. A critical study of the cases of severe diabetes described by Benedict and Joslin show a general increase of between 5 and 10 per cent in the metabolism of their patients instead of 15 per cent as claimed by them. In depancreatized dogs the metabolism rises 40 per cent above the basal level and in the phlorhizinized animal an increase of 70 per cent has been observed. Marriott has recently stated that large quantities of acetone bodies are to be found in the blood in human diabetes, but that in depancreatized dogs the quantity of acetone bodies in the blood is only slightly above the normal. It does not seem that acidosis can be the cause of the high metabolism. A much more probable stimulus to heat production lies in the largely increased quantity of amino-acids metabolized in pancreas diabetes and phlorhizin glycosuria, an explanation originally given by Rubner. Also, the increased quantity of fat in the circulating blood of diabetics may be an accessory factor in the higher metabolism observed.

In conclusion it seems that the increase in metabolism after the ingestion of food is brought about by a dual mechanism. There is an increase due to plethora in which food molecules are present in abundance, and an increase due to amino-acid stimulation as the result of which the metabolism is greatly increased without being dependent on the fuel energy of the amino-acids themselves.

Coleman and Du Bois have reported that food administration during the height of fever scarcely increases metabolism and Du Bois has found only a normal increase in exophthalmic goiter. In these cases the metabolism has already been lifted to so high a level that food hardly affects it. These are important facts for the clinician.

## VARIATION IN TUBERCULIN HYPERSENSITIVENESS DURING THE COURSE OF PULMONARY TUBERCULOSIS.<sup>1</sup>

By JAMES B. HOLMES, M. D.

Quantitative tests with tuberculin have not yet been made in such variety and in such number as to warrant definite conclusions as to their value. The value and limitations of qualitative tests are definitely known. The need today is that we should have equally accurate and full data upon the quantitative relations of the tuberculin reaction.

The condition of the body which causes a patient to react to tuberculin we call *tuberculin hypersensitiveness*. We know that it differs in different patients; some react strongly and some weakly; some patients do not react at all and certain

individuals react at one time and do not react at another. It is important to know under what conditions these variations in sensitiveness occur.

It is important to know how sensitiveness varies from week to week during the spread or arrest of a tuberculous focus, and whether there is any constant relation between the degree of hypersensitiveness present and the extent, activity and progress of the infection. And finally, it is important to know how this hypersensitiveness is influenced by tuberculin treatment. If definite quantitative relations be found to obtain, measurements of tuberculin hypersensitiveness may prove to be of much value in prognosis and treatment.

Broadly speaking, no such quantitative studies have yet

<sup>1</sup> Presented in abbreviated form before the Laennec Society of The Johns Hopkins Hospital, February 26, 1914.



been reported upon human beings. Important contributions to the study of the course of tuberculin hypersensitiveness in human beings have, however, been made by Junker, Reuschel, Hamburger, Erlandsen, White and others. These workers employed the cutaneous test, the "Stich-reaktion," and modifications of the cutaneous test.

All of these methods are unsatisfactory because of the number of factors beyond the observer's control that enter into the results. The most ambitious work with the cutaneous test has been that of Ellerman and Erlandsen abroad and of White and his associates in America. But Boardman, working here in Hamman's clinic, has shown that the variations inherent in the method itself are as great as the differences upon which the authors base their diagnostic conclusions. The results of von Pirquet, Lord, Schütz and others tend in the same direction. In its application to quantitative work, the cutaneous test must be regarded as a relatively rough test, subject to wide individual variations and, as a recent writer has said, utterly unsuited for quantitative tuberculin tests.

There remains yet a more exact method—the intracutaneous test of Mendel. In this test a measured amount of a known dilution of tuberculin is introduced into the skin in such a manner that extremely accurate readings are possible. Notable results have been obtained with this method upon experimental animals by Römer. His studies would indicate that in experimental animals the degree of reaction runs parallel with the severity of the infection. If such relations should be found to obtain in tuberculous human beings, the fact would be of very great prognostic importance.

The object of the present work is the application of this intracutaneous test to the study of the course of tuberculin hypersensitiveness in tuberculous human beings.

The work was undertaken at the suggestion of Dr. Hamman, and carried out at Eudowood Sanitarium through the courtesy of the officers of that institution.

A tray was fitted up in such manner as to facilitate accurate work. Separate bottles and syringes were provided for each dilution of tuberculin, and extreme care was taken to prevent contamination of the needles.

Solutions of tuberculin were made in the strength shown in the following table:

Bottle C = Normal Salt Sol. + ¼% Carbolic Acid.				
I.	Bottle 8	= 1/5000 mg. Tuberculin in each cc., or 1/100,000 in the 1/20 cc. dose.		
	" 7.5	=	1/33,000	" " " "
II.	" 7	= 1/500 mg. Tuberculin in each cc., or 1/10,000	" " " "	"
	" 6.5	=	1/3,300	" " " "
III.	" 6	= 1/50 mg. Tuberculin in each cc., or 1/1,000	" " " "	"
	" 5 5	=	1/330	" " " "
IV.	" 5	= 1/5 mg. Tuberculin in each cc., or 1/100	" " " "	"
Bottle 4 = 1/500 gm. Tuberculin in each cc.				
	" 3	= 1/50	" " " "	"
	" 2	= 1/5	" " " "	"
	" 1	= 1	" " " "	" i. e., Stock Tuberculin.

Bottles 5 to 8 only were represented on the tray.

Individuals reacting to the 1/20 cc. of the dilution in Bottle 8, *i. e.*, reacting to 1/100,000 mg. Tuberculin, were said to show a hypersensitiveness of Grade I; those reacting first to 1/10,000, of Grade II, and so on.

It was found that the usual reaction consisted of hyperemia

and slight infiltration about the site of injection analogous to the reaction in the cutaneous test. The area of hyperemia measured, as a rule, .75 to 2.75 cm. in diameter. This appeared usually in from 6 to 12 hours, reached its maximum in 24 to 48 hours, and, as a rule, had disappeared in a week or ten days. The reaction at the site of the control injection of sterile normal salt solution and carbolic acid consisted of a definite "traumatic" reaction, distinguishable from a mild tuberculin reaction only in that it reached its maximum in about 24 hours and had quite disappeared in 48 hours. Points of injection of tuberculin dilutions too weak to produce a tuberculin reaction presented a similar appearance and faded likewise. Postponing the reading of the test until 48 hours had elapsed removed any possibility of confusing the results of the two injections. (Where the response to a given injection was marked, it was observed that points which had responded to a former application of tuberculin presented hyperemia anew, though in lessened degree.)

The patients were all under institutional treatment. The treatment was essentially the same in each case—hygienic and dietetic. All the cases had been diagnosed as actively tuberculous; the conjunctival test had been employed in many. Each patient was carefully examined from time to time, the more frequently when there was reason to believe some change might be present. All were under my immediate supervision. A record of the temperature of each patient was available at all times, and a chart containing his subjective sensations, as recorded by himself, was available in most cases.

The tests were made at intervals of fourteen days. They were made upon the forearm, except where the patient objected to temporary disfigurement, and then upon the upper arm. Save for a tendency to a more diffuse reaction upon the upper arm, no difference was noted for the two sites.

Three injections were usually given at a distance of 3 to 4 cm. from each other; first the control solution distally, then the tuberculin dilutions in order of strength, the weaker nearer the control. In subsequent tests, an effort was made to avoid the site of earlier application, lest local hypersensitiveness should be induced.

Each individual was tested first for reaction to 1/100,000 mg., or at least to a dilution weaker than that to which it was likely he would react.

Subsequent tests were made to include the dilution to which the patient had previously reacted, and one weaker dilution, or one stronger dilution, or both, according to the peculiarities of the case, as shown in previous reactions.

Reactions were read after 48 hours; the traumatic (control) reaction had faded away by this time, whereas the tuberculin reaction was then at its height.

The size of the area of hyperemia was noted, and the presence of any unusual phenomena was sought for—unusual infiltration, central pitting, etc.

The patient was questioned about his condition before the test was made, and he was questioned again at the time of reading the test. The temperature chart was scrutinized daily.







First test, Dec. 2. Rapid general improvement thereafter. Discharged Mar. 31, "apparently cured."

(The rapid rise in tuberculin sensitiveness during the fifth and sixth week of observation, unaccompanied by clinical phenomena, in an incipient case, is unique.)

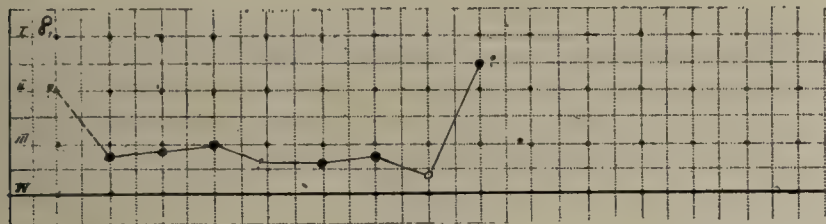


CHART 8.

CASE 8.—E. S.; female; age 17 (?). A slowly progressing case of fibroid phthisis, marked by rather frequent light attacks of pleuritic pain. Incip. II. (History misplaced in sanitarium.)

First test, Nov. 3. Very gradual progression. At the last test patient reacted strongly to 1/100 mg. and lightly to the weakest of the three dilutions used that day, 1/10,000.

Discharged, "unimproved."

CASE 9.—M. H.; female; age 13. Indefinite onset at about 10 years in what proved to be tuberculosis of the knee; pulmonary symptoms appeared in Nov., 1912. Admitted Feb. 17, 1913. Incip. II (lungs). Gaffky 0.

First test, Feb. 24. Patient showed but slight improvement during stay; the early gain of weight was lost, and pain in the knee with accompanying slight fever recurred at irregular intervals. Such an elevation in temperature was present from June 3 to 7. Discharged, June 22, "improved."

*Hypersensitiveness*: 1st test, 2.5; 2d, no reaction at 3.0; 3d, 3.5; 4th, 3.5; 6th, (?); 7th, 3.0; 8th, no reaction at 4.0; 9th, 3.0.

CASE 10.—J. McH.; male; age 17. Onset in impaired health Aug., 1911; operation for hydrocele in Jan., 1913, revealed a tuberculous omentum. Admitted Feb. 22, and rated (lungs) Incip. I. Gaffky 0.

First test, Feb. 24. Course marked by persistent tachycardia but general improvement; only slight occasional fever. Discharged, June 30, "arrested."

*Hypersensitiveness*: 1st test, 2.3; 2d, 3.0; 3d, 2.5; 4th, 2.3; 5th, 3.0; 6th, 2.9; 7th, 3.3; 8th, 3.5.

CASE 11.—L. O.; female; age 15. Large cervical gland in 1910; pleural pain and pulm. hemorrhage, 1912; frequent small hemorrhages thereafter. Admitted, Apr. 6, 1913. Incip. III.

First test, Apr. 9. Course marked by persistent pain in glands, occasional pleural pain, and slight hemorrhage, until the middle of June; improvement thereafter. Discharged, Sept. 30, 1913, "improved."

*Hypersensitiveness*: 1st test, 3.0; 2d, 2.8; 3d, 2.8; 4th, 2.8; 5th, 2.5.

CASE 12.—A. W.; male; age 24. Indefinite onset, 1911. Admitted May 1, 1913. Incip. Gaffky 0.

First test, May 5. Course uneventful; normal temperature quickly regained, and improvement steady. Discharged, Dec. 1, "favorable."

*Hypersensitiveness*: 1st test, 2.5; 2d, 2.5; 3d, 2.8.

CASE 13.—C. H.; male; age 21. Sudden onset with hemorrhage, May 1, 1913, preceded one month by subclavicular tenderness. Admitted May 5. Incip. III.

First test, May 5. Occasional slight fever; course otherwise uneventful. Discharged, July 24, "favorable."

*Hypersensitiveness*: 1st test, 2.7; 2d, 3.0; 3d, 2.7.

CASE 14.—L. H.; female; age 18. Onset with malaise (three months) followed by pulmonary hemorrhage, Apr., 1912. Admitted May, 11. Incip. III.

First test, May 5. Course uneventful. Discharged in Aug., "improved."

*Hypersensitiveness*: 1st test, no reaction at 2.5; 2d, 3.0; 3d, 3.0.

CASE 15.—E. D.; female; age 32. Indefinite history of five years' duration. Admitted in May, 1912. Moderately Advanced I. Gradual improvement throughout course.

First test, Nov. 3. Patient doing work as maid satisfactorily. Practically without symptoms.

*Hypersensitiveness*: 1st test, no reaction at 3.5; 2d, 4.0.

CASE 16.—E. L.; female; age 14. An ailing child. Indefinite onset, summer, 1912. Symptoms gradually increasing. Admitted May 5, 1913. Incip. II.

First test, May 5. Disappearance of pulmonary symptoms, but failure to gain in weight. "Improved" (June 26).

*Hypersensitiveness*: 1st test, no reaction at 3.5; 2d, 4.0.

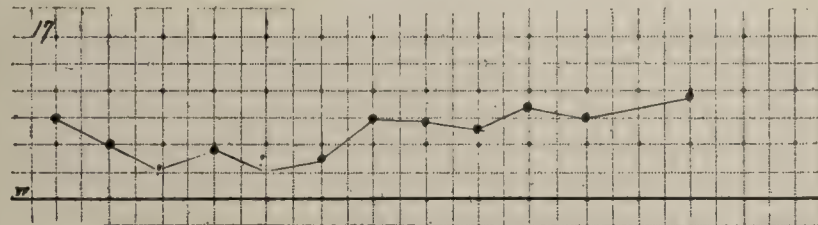


CHART 17.

CASE 17.—H. G.; male; age 28. Gradual onset during year before admission. Admitted, Nov. 30, 1912. Mod. Advanced I.

First test, Dec. 1. Rapid improvement; furunculosis during last half. Discharged, Sept. 1, 1913, "apparently cured."

CASE 18.—S. G.; male; age 17. Onset gradual, 1910; hemorrhage, May, 1912. Admitted, July, 1912. Mod. Advanced I. Gaffky 0. Superficial abscess (*S. aureus*) and frank pulmonary hemorrhage in Sept.; gradual return to normal temperature; exacerbation in early Feb.

First test, Mar. 10, 1913. Therapeutic pneumothorax induced Mar. 25; doing fairly well Apr. 26; increased cough in May. Discharged in Sept., "improved."

*Hypersensitiveness*: 1st test, no reaction at 2.0; 2d, 3.0; 3d, 3.2; 4th, 3.5; 5th, 3.2; 6th, 3.3; 7th, 3.2.

CASE 19.—J. L. M.; male; age 20. Onset gradual; attacks of "malaria" (probably genuine) at 17 and at 19; malaise in Feb., 1913; pleurisy with effusion Mar. 10; tapped. Admitted, May 1. Mod. Advanced I. Gaffky 0.

First test, May 5. Patient had chill while being transported to sanitarium; malarial organisms found in blood; prompt response to treatment and normal temperature thereafter. Discharged, June 28, "improved."

*Hypersensitiveness*: 1st test, 3.0; 2d, 3.8; 3d, 4.0.

CASE 20.—J. J.; male; age 58. Onset insidious; more or less persistent cough since early twenties; pneumonia at 24; pleurisy at 50; worse since Oct., 1911; profuse hemorrhage, in July, 1912, forced him to give up work. Admitted, Oct. 17. Mod. Advanced II. Gaffky VI.

First test, Dec. 3. Temperature, never high, slowly fell; rapid gain in weight. Discharged in December, "improved."

*Hypersensitiveness*: 1st test, (?); 2d, 3.0; 3d, 3.0; 4th, 3.2; 5th, (?).

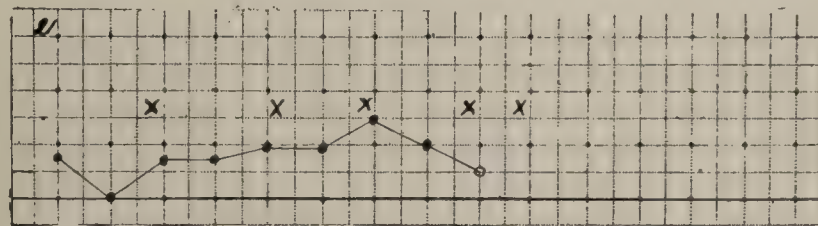


CHART 21

CASE 21.—M. L.; female; age 27. Gradual onset in spring of 1910. Pleural pain in spring of 1911; pneumonia in Aug.; steady advance



during 1911. Admitted, Aug. 22, 1912. Mod. Advanced I. Gaffky I.

First test, Nov. 17. Course marked by asthmatic attacks increasing in frequency and severity. Marked elevation of temperature at points indicated by x. Discharged, Mar. 30, 1913, "unimproved."

CASE 22.—F. H.; male; age 31. Onset indefinite; chronic cough for two years. Admitted, Oct. 27, 1912. Mod. Advanced I.

First test, Nov. 3. Course uneventful; a nervous, complaining man; Mar. 7, "gaining weight"; April 29, "uneventful"; May 26, employed about the sanitarium. Discharged, May 16, "arrested."

*Hypersensitiveness*: 1st test, (?); 2d, not made; 3d, 3.5; 4th, 3.0; 5th, 3.0; 6th, 8th and 9th, not made; 7th, 3.0; 10th, 2.5, 11th, 2.5; 12th, 2.5.

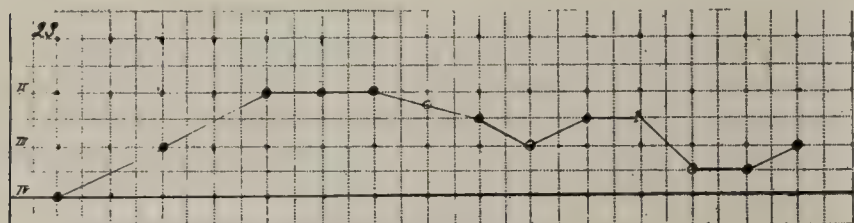


CHART 23

CASE 23.—L. D.; female; age 38. Gradual onset during 1910-12; pleurisy Mar., 1912. Admitted, Sept., 1912. Mod. Advanced I.

First test, Nov. 3. Progress unsatisfactory; neuritis in right arm, Feb. 6, and later in bed for fever and neuritis latter half of March; again in August. Progressing.

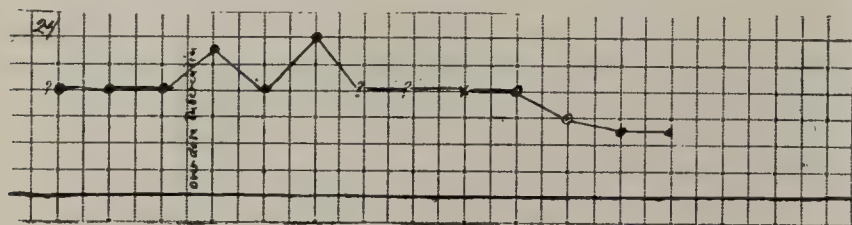


CHART 24

CASE 24.—M. P.; female; age 19. An hysterical German servant girl. Onset at age of 17; exacerbation at 18. Admitted, Nov., 1912. Mod. Advanced I. Patient submitted poorly to discipline, and resultant high fever kept her in bed much of the time. Gaffky III.

First test, Dec. 1. On Jan. 9, received an overdose of tuberculin, i. e., 1 mg. instead of 1/100,000 mg. as intended, prompt and marked local reaction, conjunctivitis (former Calmette), and middle ear exacerbation, the last persisting throughout Jan. Steady improvement thereafter; was employed as maid in May. Discharged as "arrested" in July. Now self-supporting.

CASE 25.—A. C.; male; age 36. Diagnosed at 18. Many mild exacerbations in the succeeding years; more acute exacerbation during past month. Admitted, Feb. 25, 1913. Mod. Advanced I.

First test, Mar. 10. Course uneventful. Discharged, Aug. 22, "apparently cured."

*Hypersensitiveness*: 1st test, no reaction at 3.0; 2d, 3.0; 3d, 2.8; 4th, (?); 5th, 3.4; 6th, 3.8; 7th, 3.7.

CASE 26.—A. R.; male; age 39. Pleurisy in 1905 and 1909. Cough appeared July, 1912, and health failed thereafter. Admitted, Apr. 1, 1913. Mod. Advanced II. Gaffky VI.

First test, Apr. 9. Gradual improvement. Discharged, Oct. 8, "improved."

*Hypersensitiveness*: 1st test, no reaction at 3.5; 2d, 3.2; 3d, 3.5; 4th, 3.5; 5th, 3.5.

CASE 27.—M. E.; female; age 19. Onset sudden, Jan., 1913; earlier health unusually good. Admitted, Nov. 31, 1913. Mod. Advanced I. Gaffky IX.

First test, Apr. 9. Temperature reached normal May 7; patient lost weight till Aug., then rapidly gained. Discharged, Oct. 1, "arrested."

*Hypersensitiveness*: 1st test, 3.0; 2d, 2.6; 3d, 3.0; 4th, 3.0; 5th, 3.7.

CASE 28.—M. K.; male; age 17. Onset insidious; slight dry cough in early Mar.; accompanying malaise persisted; first expectoration Apr. 1. Admitted, Apr. 3. Mod. Advanced I. Gaffky 0.

First test, Apr. 9. Temperature never elevated; rapid gain in weight; no expectoration. Discharged in July, "arrested."

*Hypersensitiveness*: 1st test, 2.7; 2d, 2.4; 3d, 3.0; 4th, 3.2; 5th, 3.2.

CASE 29.—J. B.; male; age 23. Onset acute, Jan., 1913; hemorrhages Mar. 19. Admitted, Apr. 6. Mod. Advanced I.

First test, Apr. 9. Acute attack pleurisy with effusion, May 21; recovery. Discharged, Nov. 21, "arrested."

*Hypersensitiveness*: 1st test, 2.6; 2d, 1.3; 3d, 3.0; 4th, 3.2; 5th, 3.2.

CASE 30.—J. L.; male; age 22. Onset acute with cough and pleural pain in Nov., 1912. Admitted, Dec. 7. Mod. Advanced I. Gaffky 0.

First test, Dec. 19. While in bed temperature fell rapidly; sharp elevations Jan. 27 and Feb. 13 (x); return to normal at discharge, Feb. 25; "stationary."

*Hypersensitiveness*: 1st test, 2.3; 2d, 3.2; 3d, 3.2; 4th, 3.4; 5th, 2.5; 6th, (?).

CASE 31.—A. P.; male; age 17. Onset in 1909; slight exacerbations; pleurisy in Oct., 1912. Admitted, Mar. 15, 1913. Mod. Advanced I.

First test, Mar. 24. Pain in umbilical region, probably tub. origin, Mar. 25; it disappeared gradually with improvement in patient. Loss of weight to May 23; regained in June. Discharged, July 7, "arrested."

*Hypersensitiveness*: 1st test, 3.0; 2d, 2.8; 3d, 3.0; 4th, 3.5; 5th, 4.0.

CASE 32.—J. L.; male; age 44. Long indefinite history; pleurisy in 1905; unusual winter exacerbation, Nov., 1912. Admitted, Jan. 11, 1913. Mod. Advanced I. Gaffky II.

First test, Jan. 12. Rapid gain in weight. Discharged, Mar. 14, "improved."

*Hypersensitiveness*: 1st test, no reaction at 3.0; 2d, no reaction at 3.5; 3d, 3.0; 4th, 3.0.

CASE 33.—L. M.; female; age 36. Onset indefinite, 1911; acute, Mar., 1913. Admitted, Apr. 26. Mod. Advanced I.

First test, May 5. Course uneventful save for slight pharyngitis and hyperacidity; improvement steady. Discharged, July 24, "arrested."

*Hypersensitiveness*: 1st test, 3.0; 2d, 3.3; 3d, 2.8.

CASE 34.—A. S.; male; age 55. Heavy cough in 1897, with frequent digestive disturbances thereafter; pleurisy with effusion, Feb., 1913. Admitted, May 19, 1913. Mod. Advanced I. Gaffky III.

First test, May 24. Steady improvement till attack of diarrhea with fever on Aug 9. Discharged, Mar., 1914, "arrested."

*Hypersensitiveness*: 1st test, 2.3; 2d, 3.0.

CASE 35.—C. H.; male; age 25. Onset sudden, May, 1912, with pleural pain and loss of weight. Admitted in Nov. Mod. Advanced I. Gaffky I.

First test, Apr. 21. After pleuritic pain disappeared (Dec. 21) patient gained weight for two months and held gain; course uneventful.

*Hypersensitiveness*: 1st test, (?); 2d, 3.5.



CASE 36.—T. S.; male; age 25. Cervical adenitis at 19, reappearing at 24, with failing health; acute onset, Jan., 1913. Admitted, May 5, 1913. Mod. Advanced.

First test, May 5. Improvement very slow, otherwise course uneventful. Discharged, June 19, "favorable."

*Hypersensitiveness*: 1st test, 3.0; 2d, 3.0; 3d, 3.0.

CASE 37.—J. B.; female; age 25. Onset acute with repeated hemorrhages. Admitted, June, 1912. Mod. Advanced I. Almost symptomless in Oct.; also late in Nov.

First test, Dec. 4, 1912. Patient deemed an "arrested" case. On Jan. 2, 1913, reacted to tuberculin, and had to return to bed; recovered quickly, and on 30th took up work as maid.

*Hypersensitiveness*: 1st test, no reaction at 3.0; 2d, 2.0; 3d, (?).

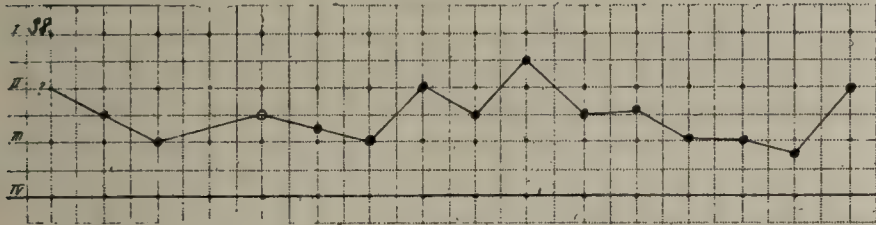


CHART 38.

CASE 38.—C. D. F.; male; age (?). Onset acute, June, 1912; progressive. Admitted, Sept. 14. Mod. Advanced II. Gaffky (?).

First test, Dec. 3. Patient confined to bed with high fever reacted severely at third test; therapeutic pneumothorax induced at fifth test, with rapid symptomatic improvement till tenth test; thereafter patient was threatened with relapses; loss of weight.

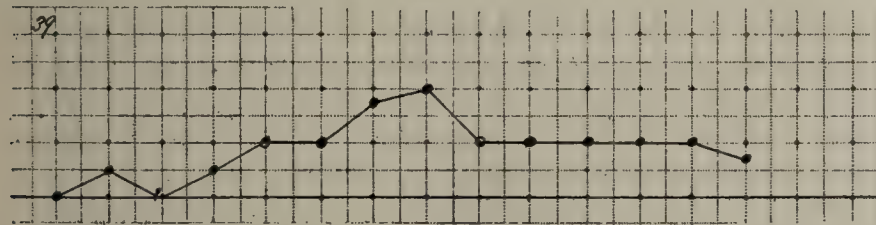


CHART 39.

CASE 39.—J. T.; male; age 40. Onset gradual in Aug., 1912; progressive to admission, Oct. 10. Mod. Advanced. Gaffky VI.

First test, Dec. 17. Therapeutic pneumothorax induced, Dec. 14; patient allowed up at fourth test; overworked himself during next week, and confined to bed until Feb. 24 (eighth test); steady improvement thereafter.

CASE 40.—R. M.; male; age 35. Tub. history of four or five years' duration. Admitted in June, 1912. Mod. Advanced II. Gaffky VII. Slight exacerbation during Sept. and more severe in Nov.; patient apparently doing poorly.

First test, Nov. 3. Some improvement recorded during next six weeks, and steady improvement thereafter. On Apr. 18 (12th test), patient (then in therapeutic tuberculin class) reacted to usual dose of tuberculin with slight local and general reaction. Discharged, May 1, "improved."

*Hypersensitiveness*: 1st test, 4.0; 2d, 3.5; 3d, 2.5; 4th, 2.5; 5th, 2.3; 6th, not made; 7th, 2.2; 8th, 2.8; 9th, 3.0; 10th, and 11th, not made; 12th, 2.6; 13th, 3.2; 14th, not made; 15th, 3.8.

CASE 41.—L. L.; female; age 22. Onset, Mar., 1911; exacerbation, 1912; gradual progress. Admitted, Feb. 14, 1913. Mod. Advanced II.

First test, Feb. 24. A neurotic girl with frequent complaints of pleural pain, lessening in frequency to discharge, Aug. 14; "arrested."

*Hypersensitiveness*: 1st test, no reaction at 3.0; 2d, 3.0; 3d, 3.0; 4th, 3.0; 5th, not made; 6th, 3.3; 7th, 3.5; 8th, 3.0.

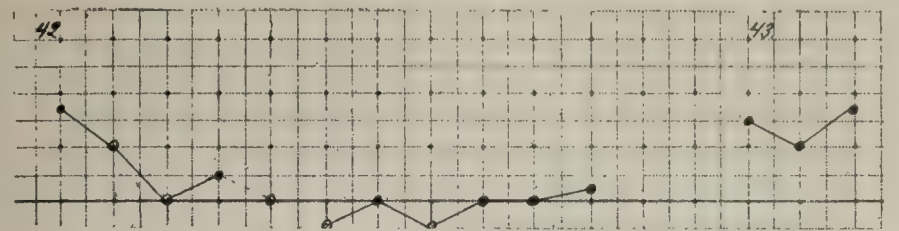


CHART 42.

CASE 42.—C. K.; female; age 29. Onset in 1907; slight exacerbation almost yearly; last one more marked, but not acute. Admitted, Jan., 1913. Mod. Advanced II.

First test, Jan. 12. Slow improvement under rest in bed till Apr. 18; allowed home for one week; pelvic inflammatory condition of low grade with temperature 99°-100°, and complaints of weakness kept patient in bed till Aug.; diminished râles. Discharged in Sept., "improved (?)."

CASE 43.—N. H.; female; age 12. Never a healthy child; "typhoid pneumonia" at 7; inmate of another sanitarium, 1909-11; exacerbation in Dec., 1912; much better on admission, Mar. 22, 1913. Mod. Advanced III.

First test, May 5. Steady and rapid improvement; without complaint on Apr. 7. Discharged, Feb., 1914, "improved."

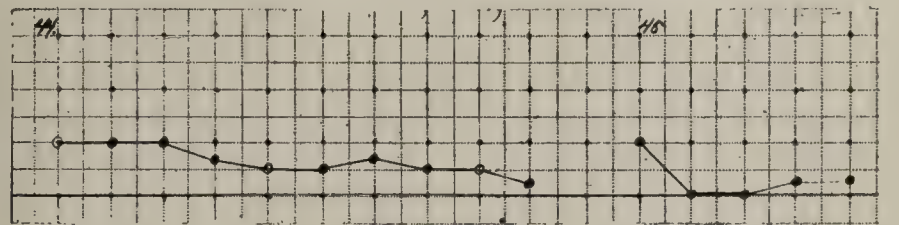


CHART 44.

CASE 44.—J. S.; male; age 51. Chronic cough for 15 years, following "typhoid pneumonia"; recent increase in symptoms. Admitted, Sept. 23, 1912. Mod. Advanced II. Gaffky VI.

First test, Jan. 27. Gradual improvement to July; small hemorrhage; loss of weight. Discharged in Aug., "unimproved."

CASE 45.—L. F.; female; age 25. Sudden onset in Aug., 1911; poor health continued without exacerbation. Admitted, Aug., 1912. Mod. Advanced II. Gaffky II.

First test, Dec. 3. Patient gained steadily in weight and improved generally; pleuritic pains vanished. Temperature normal throughout. Discharged, Jan., 1913, "arrested."

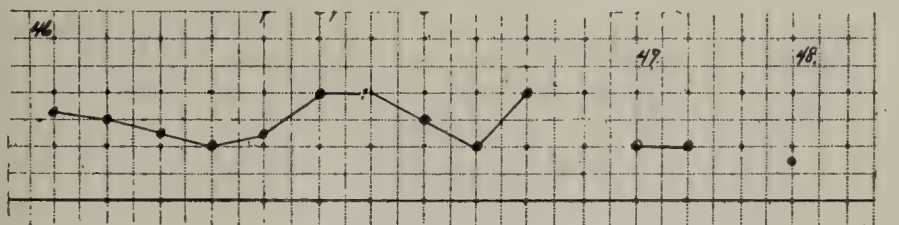


CHART 46.

CASE 46.—A. N.; female; age 20. Cervical gland appeared in 1910, and became gradually larger and more painful; slight pulmonary symptoms. Admitted, Jan. 18, 1913. Mod. Advanced II (lungs).

First test, Jan. 27. Patient confined to bed by frequent elevations of temperature (100° + to June 20); moderate gain in weight. Discharged, June 21, "improved."

CASE 47.—F. S.; female; age 10. Admitted, Mar., 1912. Mod. Advanced II. Steady improvement.

First test, Mar. 24, 1913. Pleurisy, Mar. 27. Discharged, April 3.

CASE 48.—J. N.; male; age 39. Sudden onset with malaise, cough and hemorrhage, Feb., 1913. Admitted, May 29. Mod. Advanced I.



First test, June 4. Reappearance of expectoration and pain, June 12; of pleuritic pain, June 25. Discharged, Sept. 30, "arrested."

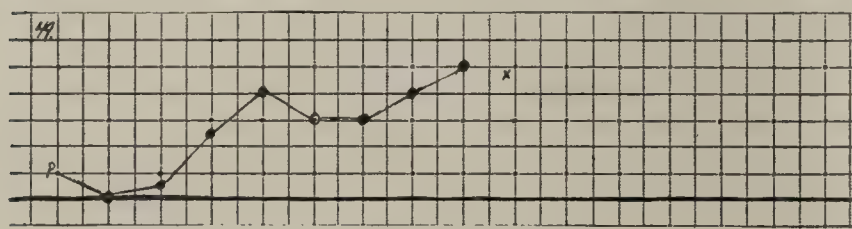


CHART 49.

CASE 49.—McK.; male; age 29. History of several years' duration. Admitted, Mar., 1912, and subjected to therapeutic pneumothorax soon after; at first improved, then gradually failed. In Dec., 1912, rated Mod. Advanced III.

First test, Dec. 17. Course marked by continued fever and gradual failure. Death (x) soon after removal to home (over-exertion?).

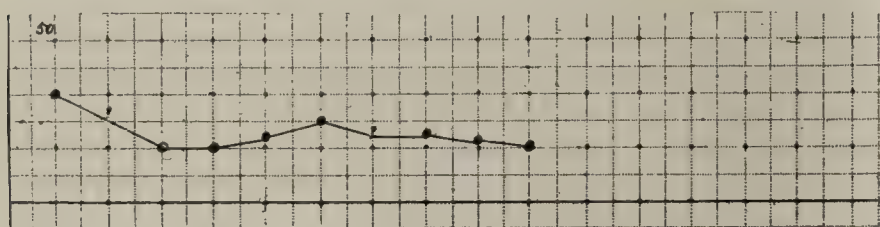


CHART 50.

CASE 50.—W. N.; male; age 34. Onset acute, Jan., 1912; symptoms increasing to admission in Nov. (acute nephritis, following debauch). Mod. Advanced III. Gaffky VII.

First test, Jan. 27. Condition improved steadily; therapeutic pneumothorax begun Mar. 22; inflations indicated by (x); only elevation of temperature, May 28 and 30. Discharged, Aug. 30, "improved."

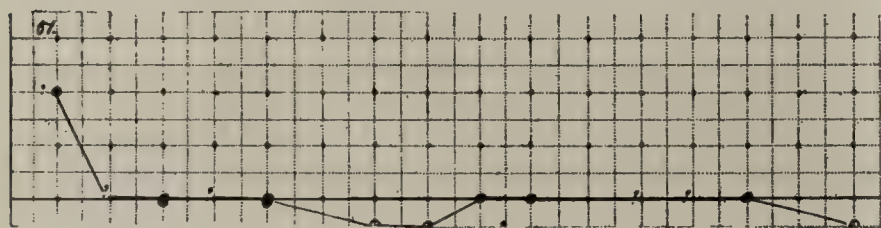


CHART 51.

CASE 51.—S. L.; female; age 20. Onset gradual, 1909; course gradually progressive. Admitted, May, 1912. Mod. Advanced I. Gaffky VI. Progressed.

First test, Nov. 3. Slow progression; therapeutic pneumothorax, April 26; result uncertain; June 14, in bed 10 days for fever, pain and increased cough.<sup>3</sup>

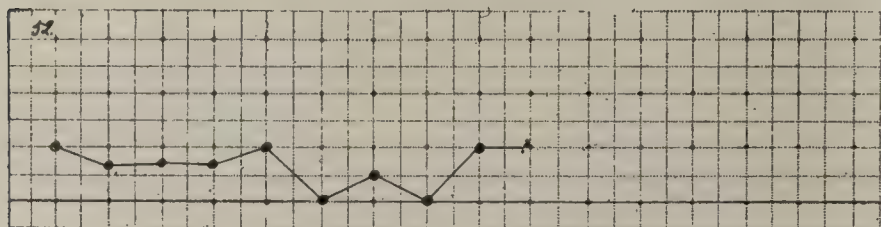


CHART 52.

CASE 52.—L. T.; male; age 39. Onset sudden, with pneumonia, 1909; subsequent impaired health; fever and cough, July, 1912. Admitted, Oct., 1912. Far Advanced I. Gaffky VII.

<sup>3</sup> The patient had completed a course of tuberculin administered in another clinic several years before the date of the first test.

First test, Nov. 3. Course marked by steady gain in weight; temperature above 100° till Dec.; thereafter below; pleuritic pain not noted after late in January. Discharged, Mar. 12, "improved."

CASE 53.—C. T.; male; age 28. Indefinite onset in June, 1911; steadily failing health till admission in June, 1912. Far Advanced I. Gaffky VII.

First test, Nov. 3. Steady gain in weight. Temperature fell to normal in Sept., and remained low until discharge; pleural pain had disappeared at that time. Discharged, Feb. 15.

Hypersensitiveness: 1st test, no reaction at 3.0; 2d, 3.0; 3d, 4th, 5th, (?); 6th, 4.0; 7th and 8th, no reaction at 4.0.

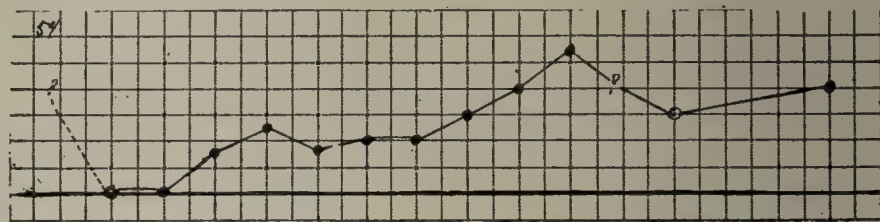


CHART 54.

CASE 54.—L. P.; female; age 55. Onset gradual; when first tested, Nov. 3, had been a patient in the hospital for several months. Far Advanced I. Gaffky (?).

First test, Nov. 3. On Dec 1, reacted violently, with markedly swollen arm; had apparently quite recovered by Dec. 15. Progressive gradual failure. In Apr. was quite ill for two weeks, all symptoms being marked.

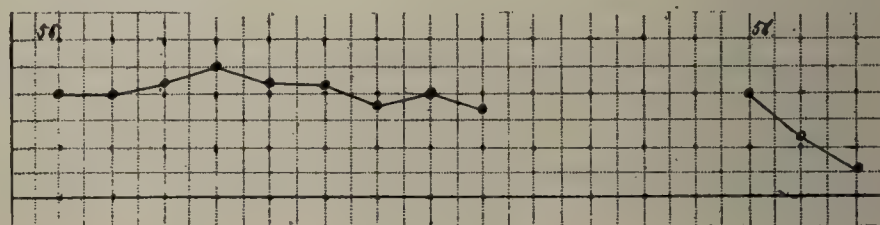


CHART 55.

CASE 55.—J. P.; male; age 43. Onset insidious, 1908; chronic cough and pleural pain followed exposure; slow progression. Admitted, Dec. 30, 1912. Far Advanced II. Gaffky VI.

First test, Jan. 27, 1913. Improved somewhat in Feb.; remained stationary in Mar.; all symptoms worse in Apr.; gradually progressing; tuberculous laryngitis.

(Between Apr. 5 and 26, patient received nearly 40 cc. of "Phylacogen." He at first experienced some relief, then became much worse.)

CASE 56.—H. F.; male; age 32. Chronic cough for four years; worse during last year. Admitted, Mar. 12, 1913. Far Advanced III. Gaffky VII.

First test, May 5. Patient improved somewhat during Apr. and May; expectorated blood in May and later ran high fever, then improved. Discharged in Sept., "improved."

CASE 57.—E. W.; female; age 26 (?). Insidious onset and slow progress during past four years; slight exacerbation during month before admission, Mar. 3, 1913. Far Advanced I.

First test, Mar. 10. Slight improvement during first two weeks, then stationary or slowly failing; did not react to 1% and 5% conjunct. test. Skiagraph showed wide-spread infiltration; sputum scanty and negative for tubercle bacilli. Discharged, June 2, "unimproved."

Hypersensitiveness: 1st test, no reaction at 3.0; 2d, 3.5; 3d, 3.5; 4th, 3.5; 5th, 3.8; 6th, 4.0.

CASE 58.—R. J.; female; age 20. Onset gradual, 1910; began to lose weight in Sept., 1912. Admitted, Feb. 25, 1913. Far Advanced I. Gaffky VII.

First test, Mar. 24. Course progressive to death, Aug. 9.



*Hypersensitiveness:* 1st test, no reaction at 3.5; 2d, 3.0; 3d, 3.0; 4th, no reaction at 3.5; 4th, 4.0.

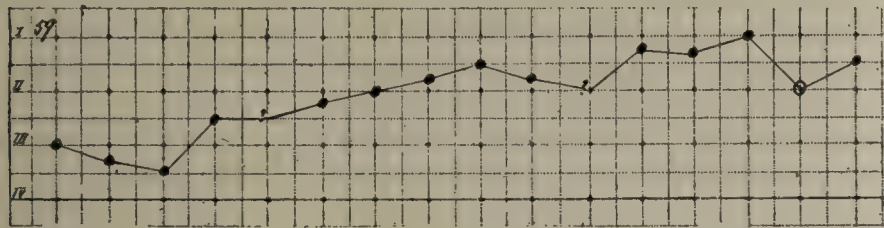


CHART 59.

CASE 59.—W. C.; male; age 22. Onset in 1911, with persistent cough. Admitted in Oct., 1912. Far Advanced I. Gaffky IV.

First test, Nov. 3. Course marked by sharp elevations of temperature associated with pleuritic pain on Dec. 4, at intervals during next two months (Jan. 22), and (slight) on Feb. 20; normal temperature and absence of pain thereafter; increasing amounts of work in Farm Colony until discharge in July.

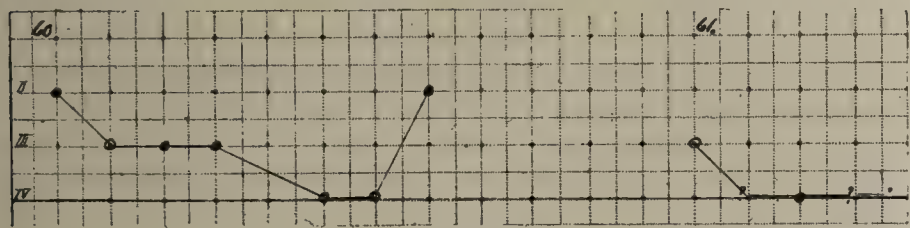


CHART 60.

CASE 60.—C. W.; male; age 32. Onset gradual, 1911; increasing symptoms and aphonia on admission, Feb. 20, 1913. Far Advanced I. Gaffky III.

First test, Feb. 24. Feb. 26, acute pain and loss of weight. Mar. 24, "much improved." Died June 25.

CASE 61.—J. D.; female; age 13. Onset in 1911; course progressive. Admitted in Sept., 1912. Far Advanced II. Gaffky (?).

First test, Nov. 3. Disease progressed to death, Dec. 23.

CASE 62.—N.; female. Far Advanced. First test, Nov. 17. "Arrested."

(History not available.)

*Hypersensitiveness:* 1st test, (?); 2d, 4.0; 3d, 3.5; 4th, (?); 5th, 3.3; 6th, 3.2; 7th, 3.0; 8th, 4.0; 9th, 3.3.

CASE 63.—R.; male. Far Advanced. First test, Jan. 27. "Improved."

(History not available.)

*Hypersensitiveness:* 1st test, 2.0; 2d, 2.0; 3d, no reaction at 2.5; 4th, no reaction at 3.0; 5th, 3.5; 6th, 3.5; 7th, 3.5; 8th, 3.5; 9th, 3.8; 10th, 4.0.

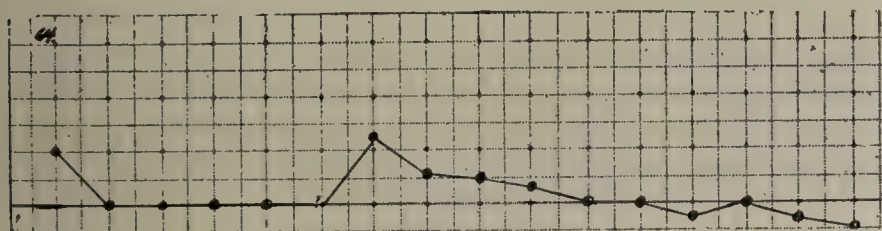
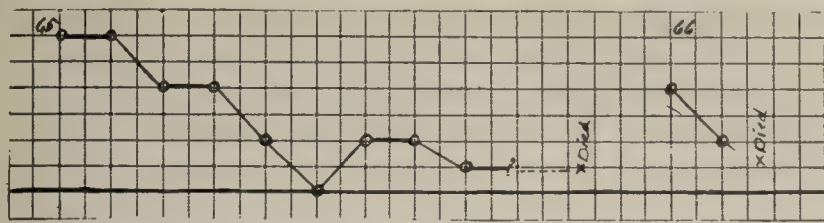


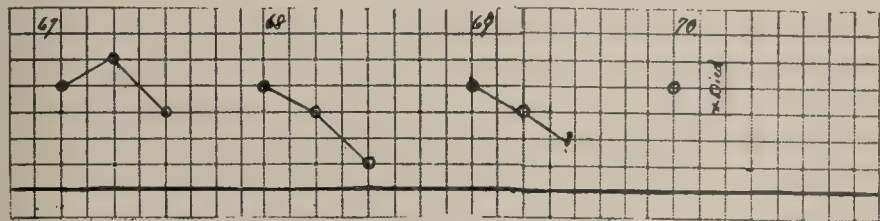
CHART 64.

CASE 64.—M. J. S.; male; age 37. Onset insidious, Oct., 1910, with persistent cough; pleural pain more frequent and more marked during last six months. Admitted, Oct., 1912. Far Advanced II. Gaffky V. Marked clubbing of fingers.

First test, Dec. 3. Improved during Nov.; fever in Dec.; improvement in Jan.; cough less. Much better in Feb., no fever; cyanosis and dyspnea marked in Apr. Discharged in Aug., "progressing."



CHARTS 65, 66.



CHARTS 67, 68, 69, 70.

CASES 65, 66, 67, 68, 69, 70.—These were far advanced cases, the patients dying.

These curves are of value only in indicating that certain grades of hypersensitiveness were not present, *i. e.*, the patient did not react to the dilution of tuberculin next above that indicated by the position of the circle (O).

*Relation of Tuberculin Hypersensitiveness to Tuberculin Therapy.*—As has been said above, 12 of the curves show also the relation existing between the grade of tuberculin hypersensitiveness found in certain patients and the dose of tuberculin tolerated by those patients when it was administered therapeutically according to Trudeau's method.

The curves of these patients are repeated below, and data as to the amount of tuberculin administered (Human Bouillon Filtrate) are given in relation to the intracutaneous tests. (When the day of the test coincided with the day of therapeutic administration and the amount given intracutaneously formed any appreciable fraction of the therapeutic dose for the day, it was reckoned as part of that dose.)

These curves fail to show any relation between the amount of tuberculin tolerated when administered subcutaneously by Trudeau's method and the grade of hypersensitiveness present in that patient as measured by the intracutaneous test. A glance at the curves shows this.

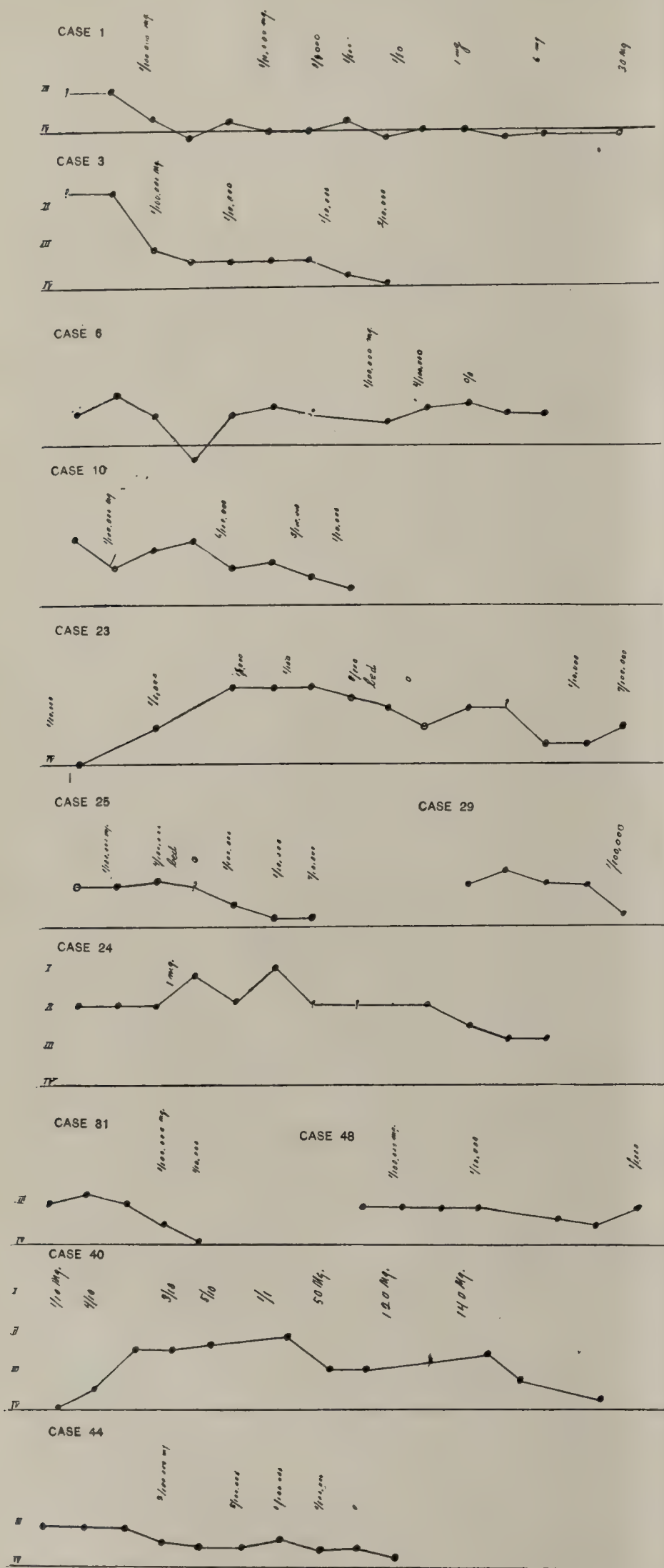
These charts show that patients with incipient pulmonary tuberculosis usually entered the sanitarium while showing marked hypersensitiveness to tuberculin, and that this hypersensitiveness diminished rapidly under rest in bed and improved diet.

If the patient did well, the hypersensitiveness fell and remained down; if he did badly, it rose, falling again as the patient improved.

The curves of the advanced cases show that the rise in hypersensitiveness earlier observed, increases up to a maximum, that varies with the individual perhaps, as the disease progresses, and then falls. (The patient may even fail to react to the maximum dose employed in this study, *i. e.*, .01 mg.)

The curve of hypersensitiveness in an early and improving case of pulmonary tuberculosis, and that in an advanced and progressing case, may be similar in appearance, and are to





be distinguished one from the other only with the clinical history at hand.

Cases that are progressing slowly, give a long, gradual rise, *cf.*, Case 54; those progressing rapidly may give a sharper, more abrupt rise, *cf.*, Case 49.

Moderately advanced cases yield varied curves with rises and falls corresponding roughly with the patient's condition.

Such patients usually entered the institution during or soon after an exacerbation and presented elevated hypersensitiveness; this fell as they responded to treatment, rose when they failed to do so.

The degree of hypersensitiveness present in an individual apparently bears no relation to the amount of pulmonary involvement present; the degree of hypersensitiveness does appear to be related to the activity of the focus and to the patient's response.

Cases of quiescent incipient pulmonary tuberculosis, and arrested advanced pulmonary tuberculosis and dying patients may all present the same degree of hypersensitiveness on a given day.

No definite interval between the appearance of an exacerbation and the development of hypersensitiveness was observed. Where the case was carefully watched the rise in hypersensitiveness never gave warning of an approaching exacerbation; it rather confirmed the opinion that such was in progress.

It is difficult to generalize even where many examples are before one. Certain glaring exceptions are apparent, as for example, Case 7, where steady clinical improvement was accompanied by a rise in hypersensitiveness, and perhaps also, Case 17.<sup>4</sup>

However, a careful review of the curves here presented seems to warrant the following conclusions:

**Conclusions.**—Individuals suffering from pulmonary tuberculosis present marked tuberculin hypersensitiveness soon after the clinical onset of the disease. This hypersensitiveness diminishes if they improve and fluctuates or remains stationary, if they do not improve. More advanced cases, in time of exacerbation, present this elevated hypersensitiveness again; it rises or falls, following more or less closely the clinical course of the disease. Toward death, it may rise much higher, and then fall until it fails entirely.

In closing I wish to express my thanks to Dr. Louis V. Hamman for suggesting the present study and for his continued interest in the work.

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<sup>4</sup> In some cases the explanation is doubtless to be sought in the interaction of toxins derived from secondary infections in the pulmonary focus or elsewhere. Von Pirquet, Ellerman and Erlandsen, and many others have noted the marked effect of certain secondary infections upon tuberculin hypersensitiveness. No clear example of this appeared in the present study.



# THE RELATION OF THE SENSORY NERVES TO INFLAMMATION.

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AND

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The relation of the sensory nerves to inflammation is an unsettled question. It is generally believed that an area deprived of its sensory nerve supply is more susceptible to injury, but recent observations tend to show that the inflammatory reaction in such an area is beneficially modified. In the following paper the literature will first be reviewed and then certain experimental and clinical data which have a bearing upon this subject will be presented.

Head's observations<sup>1</sup> (1905) on the regeneration of sensory nerves in his own arm are of importance. He found that following section of the sensory nerve the anæsthetic area was particularly prone to infections which healed slowly. With the regeneration of the protopathic nerve fibres, which were the first to regenerate, the lesions cleared up rapidly in this area, and the increased susceptibility to infection ceased. Spiess<sup>2</sup> (1906) emphasized the effect of local anæsthesia upon inflammations. He applied local anæsthetics to inflamed areas and operative wounds of the nose and throat, and concluded that the course of the inflammations was shortened and that the wound healing was much more rapid.

Bruce<sup>3</sup> (1910), working in Meyer's laboratory, studied by experimental methods the influence of the sensory nerves upon inflammation. After producing peripheral anæsthesia by section of the cord, he found no modification of the inflammatory reaction to croton oil in the anæsthetic area. After section of the posterior root at a point proximal to the ganglion there was likewise no deviation from the normal reaction. This was also found to be the case if the posterior root was sectioned at a point distal from the ganglion and the reaction tried immediately after the operation. On the other hand, a decided difference in the inflammatory reaction, as compared with the normal, was found if the nerve sectioned at a point peripheral from the ganglion was allowed to degenerate before the reaction was tried. At this time he obtained a complete suppression of the reaction in the anæsthetic area. The nerve sectioned in this experiment was the ophthalmic branch of the trigeminus. Bruce also observed that in eyes made anæsthetic by the local application of alypin, practically no reaction to irritants was produced. From these experiments he concluded that the sensory nerve endings were the elements that controlled the inflammatory reaction, and that this control was probably exerted by an axone reflex between the sensory nerve endings and the blood vessels.

Jacobson<sup>4</sup> (1910) found that in denervated areas there was no deviation from the normal repair of wounds. She concluded that trophic disturbances could be explained by changes in the vasomotor system with increased susceptibility to infection, or by the loss of the protective reflexes from lack of sensibility to injurious agents. Recently Januschka<sup>5</sup>

(1913) has shown that many substances including calcium lactate, magnesium sulphate, sodium salicylate, phenacetin, quinin, morphin, chloral, adrenalin, and ether modified the inflammatory reaction to mustard oil in the eye. Basing his conclusions upon the previous experiments of Bruce, Januschka concluded that this influence was probably due to the action of the drugs upon the sensory nerve endings.

The definite results of Bruce and Januschka indicating an amelioration of the inflammatory reaction, as contrasted with the generally accepted idea that there is an increased susceptibility to injury in parts deprived of their sensory nerve supply, have led the authors to repeat in part their experiments.

## EXPERIMENTS.

The experiments to be reported may be divided into two main groups. In the first an attempt was made to repeat and amplify the observations based on the animal experiments recorded in the literature: while in the second group advantage was taken of various lesions which had produced areas of anæsthesia in patients admitted to the surgical and medical clinics of The Johns Hopkins Hospital.

### GROUP I.

In Group I the inflammatory reaction was studied: (A) Following section and degeneration of the ophthalmic branch of the trigeminus nerve; (B) after the application of local anæsthetics; and (C) following the administration of morphin and chloral.

(A) The procedure for sectioning the ophthalmic branch of the trigeminus was as follows: The operations were always performed under aseptic precautions and ether anæsthesia. The right side was arbitrarily chosen for the operative procedure in all cases. A transverse incision was made across the head between the eyes and the base of the ears, which was extended on the right side to 1 cm. below the maxillary process. The skin was retracted and the underlying fascia, muscle, and periosteum were cut along the line of the skin incision. With a trephine a small button was removed from the skull on the right side as low down as possible. In the removal of this button great care was exercised not to damage the dura. The dura was then freed from the skull in the direction of the Gasserian ganglion and the opening in the skull enlarged with a rongeur. The brain and dura were retracted from the skull with a small section lifter until the nerve came into sight.

A considerable number of operations were unsuccessful, either on account of excessive bleeding, or because the ophthalmic branch of the trigeminus gave off a small radicle close to the ganglion, which was not reached at the operation. The



animals stood the operation well, post-operative infection being unusual. Half-grown rabbits were more satisfactory to operate upon, because it was much easier to cut through the bone in the region of the nerve. It was not found necessary to treat the eye of the side on which the operation was performed for post-operative conjunctivitis. This usually occurred two or three days after operation, but was slight in amount and cleared up in a day or two without injury to the eye. Eight of the operations were successful.

The inflammatory reaction of the anæsthetic eye to mustard seed oil, the normal eye being used as a control, was studied at periods of from eight days to three months after the operation. The protocol of rabbit No. 10 will be given in full as an example. Two other protocols will be given in abstract form.

#### PROTOCOL.

Rabbit No. 10. 1/18/13: 10.30 a. m. Operation with section of the ophthalmic branch of the N. trigeminus on the right side.

4.30 p. m. The animal has completely recovered. The right eye is anæsthetic.

1/20: The right eye is injected and there is a purulent exudate present. The eye is irrigated with normal salt solution.

1/22: There is a slight corneal erosion and injection of the vessels. Salt irrigation.

1/23: The right eye is injected and a purulent exudate and corneal ulcer are present. Irrigated as before.

1/26: Eyes are without signs of inflammation except for a corneal opacity in the right eye. At 12.15 p. m., one drop of mustard seed oil is placed in each eye.

#### RIGHT EYE.

1/26: 12.25 p. m. Slight injection and œdema.

12.35 p. m. Slight injection and marked œdema.

12.45 p. m. The œdema of the upper lid is more marked and there is injection of the vessels.

12.55 p. m. Very marked œdema of the upper lid and definite œdema of the pericorneal conjunctiva. The vessels show indistinct injection in these areas, but in the lower lid, where the œdema is less, the injection is more marked.

1.05 p. m. The œdema is a little increased, and the vessels are a little less distinct.

1.15 p. m. Extreme œdema of the upper lid and of the sclera.

1.30 p. m. Extreme œdema of the upper lid and sclera; the injection of the lower lid is less marked.

1.45 p. m. No apparent change.

2 p. m. No apparent change.

2.15 p. m. œdema a little less marked. The vessels are more clearly seen than in the left eye.

#### LEFT EYE.

A slight injection is present.

Injection is a little more marked than before.

Little change.

Marked injection and a definite œdema.

A definite œdema with injection of the vessels and a few flecks of exudate.

The œdema has increased a little and the injection is well marked.

Marked œdema of the upper lid and sclera with definite œdema of the lower lid. The injection is less marked.

The œdema has increased but the injection is less apparent.

Extreme œdema of the upper lid and sclera with well-marked œdema of the lower lid. The injection is very slight.

Extreme œdema of both lids and sclera. Vessels indistinct.

#### RIGHT EYE.

3.15 p. m. Marked œdema. The injection is not very apparent.

4.45 p. m. The œdema has diminished. The injection is more marked than in the left eye.

8 p. m. The œdema is much less than in the left eye and less than at 4.45. Injection more apparent. Exudate present.

1/27: 10 a. m. Very slight œdema and injection of the vessels with a few small hemorrhages. Injection of the pericorneal vessels. An exudate is present.

1/28: 12 m. There is very slight œdema with slight injection of the vessels.

1/29: Slight clouding of the cornea and only slight injection or œdema.

1/30: 10.30 a. m. Practically no injection or œdema and very slight exudate.

2/6: 2 p. m. Normal.

2/10: Normal.

2/14: Normal.

2/23: Normal.

2/30: Normal.

4/25: Three months and seven days after the operation the eyes are normal except for an opacity in the left cornea. The reaction is now repeated.

2.40 p. m. One drop of mustard seed oil is placed in each eye.

#### RIGHT EYE.

2.50 p. m. Lacrymation and injection are marked.

3 p. m. œdema and injection slight. Cloudy exudate present.

3.10 p. m. Diffuse injection. The œdema is marked but less than in the left eye. Exudate present.

3.30 p. m. Diffuse injection. œdema not much changed. Exudate about the same.

4 p. m. œdema a little increased. The injection is diffuse.

#### LEFT EYE.

œdema very extreme; vessels very indistinct.

The œdema has very slightly diminished. Vessels a little more prominent.

The œdema has diminished but is well marked. The vessels are less distinct than those in the right eye. An abundant exudate.

Definite œdema. Injection of the vessels with a few small hemorrhages. A thick, white exudate is present.

Intense injection of the vessels with hemorrhages and a thick purulent exudate. Marked œdema of the lids.

Deep injection with diffuse reddening and slight œdema. Opacity of the cornea is present. The exudate has somewhat diminished.

Little change from 1/29.

The injection is still very marked and a thick exudate is present. In the center of the cornea is an ulcer through which protrudes the lens.

Little change.

Purulent exudate diminished. Vessels extending well into the cornea. Injection diminished.

The injection is slight and the cornea is clearing.

Normal except for a corneal opacity. Vessels not visible in the cornea.

#### LEFT EYE.

There are definite œdema, slight injection and lacrymation.

The œdema has increased and is very marked. Injection slight. There is a cloudy exudate.

The œdema has increased and is very marked. Diffuse injection and exudate.

The œdema has increased and there is a diffuse injection. Exudate about the same.

The œdema is increased and the injection is diffuse.



RIGHT EYE.

4.55 p. m. The œdema increased but not extreme. The vessels are little changed. Corneal clouding is present.

4/26: 10.15 a. m. Intense injection and slight œdema. Flecks of exudate are present.

4/27: 10.30 a. m. There is a brilliant pericorneal injection with small vessels extending into the cornea 1.5 mm. Slight exudate and œdema with clouding of the cornea.

4/28: 3. p. m. The injection is marked but diminished and the cornea is cloudy with vessels extending into it. Slight exudate and œdema.

4/29: 10.30 a. m. There are marked injection, slight œdema, corneal clouding, and purulent exudate.

5/1: 9.30 a. m. There is a brilliant injection with extension of the vessels farther into the cornea. Slight œdema and exudate are present.

5/2: Little change.

5/3: 3.30 p. m. The injection is diminished but still marked. Slight exudate and œdema.

5/5: 9. 40 a. m. The injection is well marked. Slight exudate and œdema.

5/10: 3 p. m. Slight injection and corneal clouding with barely visible vessels extending into it.

5/21: Slight injection. The cornea is clear except for minute vessels. Slight exudate.

5/27: Definite injection and exudate.

5/28: Dead. Autopsy: The ophthalmic nerve has grown together so that it is impossible to tell whether it was sectioned at operation or not. Other animals in which the severed ends of the nerve were found to be separated, however, gave the same reaction as that seen eight days after operation in Rabbit No. 10.

*Summary of Protocol.*—The right ophthalmic branch of the trigeminus was sectioned at a point distal from the Gasserian ganglion. Mustard seed oil was applied to the eyes on two successive occasions, the first being eight days after operation, this period being allowed for the degeneration of the nerve to take place. At the time of the application the eyes were apparently normal except for anæsthesia of the right eye. At first the inflammation was equal in the two eyes, but on the fifth day it had subsided to normal in the anæsthetic eye. The control eye continued to show some reaction and the inflammation did not subside for a month. Three months and seven days after the operation the eyes were normal and mus-

LEFT EYE.

œdema very prominent but injection less evident.

Same as right eye.

The injection is brilliant with barely visible vessels extending into the cornea. There is also a purulent exudate with clouding of the cornea.

The injection is much more than in the right eye. There is corneal clouding and the exudate is more than in the right eye. Slight œdema.

The injection is a little less than in the right eye; the œdema is a little more. The corneal clouding and purulent exudate are the same.

Same as in right eye.

Same as in right eye.

Same as in right eye.

Same as in right eye.

There is definite injection. The vessels extending into the cornea are well seen.

The same as in the right eye except that the injection is a little more.

The same as in the right eye.

tard seed oil was again applied. The reaction was now similar in the two eyes and continued for about a month.

*Summary of Protocol of Rabbit No. 49.*—Thirty-five days after section of the ophthalmic branch of the trigeminus, mustard seed oil was applied to both eyes. On the anæsthetic side a well-marked reaction was obtained, which began to subside on the third day, the return to normal taking place by the sixth day after the application of the irritant. The control eye up to the time of the animal's death, on the eighth day, showed a well-marked reaction.

*Summary of Protocol of Rabbit No. 15.*—Two months after operative section of the ophthalmic branch of the trigeminus nerve mustard seed oil was placed in each eye. The reaction in the anæsthetic eye was well marked for ten days, a return to normal being noted on the fifteenth day. An inflammatory reaction was still present in the control eye at the end of one month.

(B) The experiments with local anæsthesia were carried out according to the method employed by Bruce. A 10 per cent solution of alypin was used to produce anæsthesia. One drop of this solution was placed in one eye of a rabbit every 10 minutes throughout the experiment, the other eye being saved for control. Following the third drop of the anæsthetic, one drop of mustard seed oil was placed in each eye. Five of these experiments were carried out, all of which gave similar results. A sample protocol follows.

PROTOCOL.

Rabbit No. 2: Both eyes are normal. One drop of alypin is placed in the right eye at 10.10 a. m., and at ten-minute intervals throughout the experiment from this time. At 10.30, the right eye being anæsthetic, one drop of mustard seed oil is placed in each eye.

RIGHT EYE.

10.40 a. m. Slight œdema and injection.

10.50 a. m. No change.

11 a. m. The injection is a little more marked. The œdema is unchanged and there are a few flecks of exudate.

11.10 a. m. The injection is a little less prominent and the œdema unchanged.

11.30 a. m. Little change.

11.40 a. m. Definite œdema and injection with slight exudate.

LEFT EYE.

Slight œdema and injection.

œdema and injection a little more marked.

The œdema has increased and is a little more marked than in the right eye. The injection is a little less apparent than in the right eye. There are a few flecks of exudate.

The œdema has slightly increased; injection much more prominent.

The œdema and injection have increased but very little.

Well-marked œdema and injection with slight exudate.

From the foregoing protocol it will be seen that a definite reaction was obtained to mustard seed oil in the eye made anæsthetic by alypin.

(C) In the third division of the animal experiments, the effect of chloral and morphin upon the mustard seed oil reaction in the eye was studied. The method and dosage employed were similar to those of Januschka. The protocols follow.



Rabbit 1m. Weight 2400 gms. A 5 per cent solution of morphine sulphate given in three doses: at 3 p. m., 10 cc.; at 3.30 p. m., 10 cc.; at 4.07 p. m., 10 cc.; the drug being given by subcutaneous injection. At 4.02 p. m. mustard seed oil is placed in one eye.

4.13 p. m. Slight injection.

4.23 " " "

4.35 " " "

4.45 " " "

4.55 " " "

5.10 " " "

The next morning the animal was found dead.

Rabbit 1c. Weight 1440 gms. The eyes are normal. At 3.05 p. m., 11 cc. of a 10 per cent solution of chloral hydrate is given by stomach tube. At 3.35 p. m., the corneal reflex is not present and one drop of mustard seed oil is placed in one eye.

3.45 p. m. Very slight injection.

3.55 " " " "

4.10 " Slight injection and very slight œdema.

4.25 " " " " " " " "

4.40 " Well-marked œdema with injection obscured.

5.00 " œdema little increased.

On comparing the reaction to mustard seed oil in the eyes of the animals treated with morphin and chloral with the reaction in the control eyes in the other experiments, it will be seen that a slight but definite deviation from the normal reaction is present. Only one of each of these experiments was carried out.

#### DISCUSSION.

In the eye in which anæsthesia has been produced by section of the ophthalmic branch of the trigeminus and the nerve allowed to degenerate, it is seen that a well-marked inflammatory reaction results, following chemical irritation. This reaction does not differ from that in the control eye so long as it lasts. There may be more œdema at first, which obscures the injection, or the œdema may be a little slower to appear than in the control eye, but there is no real difference. The change begins to appear from the third to the sixth day of the inflammation, after which the reaction subsides and disappears. According to the theory of Bruce there should be no reaction in the anæsthetic eye, when the sensory nerve endings have been eliminated. These conditions have been fulfilled and yet an inflammatory reaction is obtained. It would, therefore, seem that some other factor or factors are involved in the production of the inflammatory reaction besides the sensory nerve endings.

In this type of anæsthesia the eye returns to normal by about the sixth day. With the kind of inflammatory agent used no increased susceptibility to the injury was noted, but an apparently beneficial effect was found in the removal, by degeneration, of the sensory nerve endings. The observations of Head indicate that, when in such areas the injurious agents are bacteria, the results are not beneficial but decidedly otherwise.

In the experiments carried out two and three months after section of the ophthalmic branch of the trigeminus, it was noted that the reaction in the eye took longer to subside. Two months after the operation the reaction did not subside until

15 days after the irritant was applied, while three months after the operation the reaction was normal. Since at operation it was impossible to separate the severed ends of the nerve by any distance, these differences in the reaction, as compared to that a shorter time after section, can probably be explained by regeneration of the nerve fibres.

In the eyes made anæsthetic by the local application of alypin a definite inflammatory reaction was noted when mustard seed oil was introduced. This reaction may have differed slightly from that in the control eyes, but this difference seemed negligible. The results obtained with this type of anæsthesia coincided with those obtained in the experiments in which the nerve was allowed to degenerate.

From these experiments little support for the theory of an axone reflex is found, since in all cases in which the sensory nerve endings were eliminated a well-marked inflammatory reaction resulted when the irritant was applied.

The experiments, in which the effect of morphin and chloral upon the mustard seed oil reaction in the eye was studied, showed a quite definite modification of the inflammatory reaction when these drugs were administered subcutaneously and by mouth respectively. From the evidence obtained in the experiments bearing upon the reaction in anæsthetic areas, it would seem that this effect must be due to an action of these drugs upon some other element besides the sensory nerve endings. The doses given were maximal and the vitality of the animals was greatly reduced. This point of course must be considered in drawing conclusions.

#### GROUP II.

The experiments in Group II, in which the inflammatory reaction was studied in patients having anæsthetic areas, fall into three sub-groups according to the type of lesion manifested. Included in (a) are the cases of anæsthesia due to injury to the peripheral nerve following operation or trauma. The reaction in these cases was not tried until enough time had elapsed for the sensory nerves to degenerate. In (b) are patients suffering from anæsthesia due to lesions of the central nervous system. In (c) are included two cases of hysterical anæsthesia, one case of tabes, and one in which rather large doses of sodium salicylate were being employed.

The method employed in these experiments was as follows: Small pieces of cantharides plaster, 5 mm. square, were used to produce the inflammatory reaction. These plasters were applied to the anæsthetic area, and to an area of normal sensation, respectively. The control area was usually in a position corresponding to that of the anæsthetic area. In applying the plaster the skin was moistened with a 1 per cent acetic acid solution and the plaster was coated with a thin layer of vaseline. After three hours or longer the plasters were removed and observations were made as shown in the accompanying charts.

The inflammatory reaction after three hours was usually quite definite. In identical normal areas this reaction showed slight variations, that were doubtless due to slight differences in the amount of cantharides which remained after removal of



1. LESIONS OF PERIPHERAL NERVOUS SYSTEM.

Case.	Name.	Age.	Sex.	Condition.	Anæsthesia.										Location of plaster.	Plaster applied.	Duration.	On removal.	12 hrs. or less.	24 hrs. or less.	48 hrs. or less.	72 hrs.
					Complete.			Partial.			Dura- tion.											
					Pain.	Temp.	Touch.	Pain.	Temp.	Touch.												
1	W. K. Surg. No. 33958	40	M.	Cirrhosis of liver. Rt. rectus incision (2, 19, '14). Omentopexy. Anæsthetic area 2.5 cm. in diam., to left of incision 5 cm. above umbilicus.	+	+	+	....	....	....	....	40 days	A. A. Left of incision.	4, 1, '14 10 a.m.	3 hrs.	Excoriat'n and faint reddening. Blister and faint reddening.	7 hrs. Vesicle with slight zone of reddening. Flush more prominent. Zone a little larger.	Scab. Induration of narrow ring of reddening. Slight induration and perhaps more reddening.	Narrow zone of flushing.			
2	M. T. Surg. No. 34219	49	F.	Complete left breast operation (3, 30, '14). Anæsthesia post. surface left arm.	+	+	+	....	....	....	....	28 days	A. A. Post. surface of left arm. N. A. Ant. surface of left arm.	4, 27, '14 10.15 a.m.	3 hrs.	No reaction.... No reaction....	No reaction..... No reaction.....	No reaction.... No reaction....				
3	M. M. Surg. No. 33706	17	F.	Exophthalmic goitre. Lobectomy (3, 28, '14). Anæsthetic area rt. side of neck just below thyroid incision.	+	+	+	....	....	....	....	1 mo.	A. A. Right side of neck below incision. N. A. Same side above incision.	4, 24, '14 10 a.m.	3 hrs.	Slight blister. Faint flush. Slight blister. Faint flush.	8 hrs. Large blister. Zone of reaction smaller.	Blister gone, slight flush. Blister gone, a little less flushing.	Faint flush, slight excoriation of skin. No reaction....	Slight excoriation. No reaction.		
4	T. C. Surg. No. 34024	29	M.	Varicose veins of rt. leg excised (3, 2, '14). Anæsthetic area just to left of incision in lower leg 3 cm. in diam.	+	+	+	....	....	....	....	1 mo.	A. A. Below knee on rt. leg. N. A. Corresponding place on left leg.	4, 1, '14 10.20 a.m.	2 3/4 hrs.	No reaction.... Faint flush, if any.	6 hrs. No reaction. No reaction.	Slight excoriation. About the same ...	No reaction. .. No reaction....			
5	G. M. Surg. No. 33448	30	F.	Exophthalmic goitre. Lobectomy (2, 5, '14). Anæsthetic area 2 cm. in diam., in midline just above incision.	+	+	+	....	....	....	....	23 days	A. A. Midline just above incision. N. A. Right side of neck.	2, 28, '14 10 a.m.	3 hrs.	Faint zone of flushing. Relatively br'd. line of flushing.	6 hrs. Slight zone of flushing. Slight swelling and reddening definitely more.	Definite swelling and small zone of flushing. Flushing larger and more intense. Difference less.	Faint flush and swelling. More active flush. Slight swelling.	Swelling slight, faint flush. Reaction more.		
6	F. H. Surg. No. 33853	63	M.	Shoulder-girdle amputation for sarcoma of humerus (2, 18, '14). Large anæsthetic area in post. flap.	+	+	+	....	....	....	....	16 days	A. A. Large flap from left back. N. A. Left back...	2, 28, '14 9.25 a.m.	3 1/2 hrs.	Slight moist're. Definite flush, little blister.	7 hrs. Slight reddening and swelling. Blistering. Reddening more marked, definite swelling.	Very faint flush.... Wide zone flushing. Definite swelling.	Very slight flush. More intense reaction. Swelling.			
7	L. P. Surg. No. 33755	24	M.	Rupture of brachial plexus (8, 28, '13.) Complete paralysis of left arm below elbow.	+	+	+	....	....	....	....	5 mos.	A. A. Left forearm, palmar surface. N. A. Corresponding place on rt. arm.	1, 27, '14 2.45 p.m.	6 hrs.	Blister, very faint flush. .....	..... .....	21 hrs. Blister. Flush very slight. Blister, swelling, slightly more flushing.	44 hrs. Blister and slight flush.	No change. No change.		
8	T. F. C. Surg. No. 34399	37	M.	Fracture of left elbow (10, 20, '13). Anæsthesia of left little finger and half of ring finger.	+	+	+	....	....	....	....	6 mos.	A. A. Ulnar surface of left little finger. N. A. Corresponding place on rt. little finger.	4, 24, '14 11 a.m.	9 hrs.	No reaction.... No reaction....	No reaction..... No reaction.....	No reaction.... No reaction....	No reaction.... No reaction....	No reaction. No reaction.		
9	J. G. G. Surg. No. 34295	23	M.	Right rectus incision (4, 8, '14). Anæsthetic area size of dollar mesial to incision.	+	+	+	....	....	....	....	33 days	A. A. Mesial to incision. N. A. Lateral to incision.	5, 11, '14 10 a.m.	4 1/2 hrs.	Faint flush, moist base. A little more reddening.	Small blister and slight zone of injection. Large blister, wide zone of reddening. Some swelling.	Blister. Very faint flush. Large blister. Flushing more.				

A. A. = Anæsthetic areas. N. A. = Nonanæsthetic areas.



2. LESIONS OF CENTRAL NERVOUS SYSTEM.

Name.	Age.	Sex.	Condition.	Anæsthesia.						Location of plaster.	Plaster applied.	Duration.	On removal.	24 hrs. —.	24 hrs. +.	48 hrs. +.	72 hrs.
				Complete.			Partial.										
				Pain.	Temp.	Touch.	Pain.	Temp.	Touch.								
C. T. R. Surg. No. 33767	46	M.	Cerebral tumor. Onset of symptoms 12, 1, '13. Dec. 31 diminished sensation over entire rt. side of body. Operation (1, 6, '14). Removal of glioma from post-Rolandic area.	....	....	....	+	+	+	1 mo.	5 hrs.	Blister .....	17 hrs. Very slight induration.	Induration slight. Very slight flushing. Blister still intact.	Slight reddening and induration.		
J. B. Surg. No. 33874	21	M.	Cerebellar cyst. Symptoms of tumor for 1 yr., recently on left side of body. Hyperesthesia on left side, arm and leg.	....	....	....	+	+	+	?	3¾ hrs.	Small blister (broken) with small zone of reddening.	9 hrs. Well-marked swelling and flushing.	28 hrs. Slight swelling, with flush.	Small scab with zone of reaction.	Very faint reaction.	
C. K. W. Surg. No. 34405	46	M.	Fracture of spine (sacrum) (2, 14, '13). Riding breeches anæsthesia. Impaired motor function for 1 mo. following injury.	+	+	+	....	....	....	15 mos.	3 hrs.	Faint flush.....	8 hrs. Blister, wide flush.	Injection, large blister.	Faint narrow flush about blister.	Subsiding.	
M. J. Surg. No. 32127	19	F.	Tumor in thoracic region. Numbness below waist since Jan., 1914. Backache for 1 year. Admitted Feb. 12. Anæsthesia partial.	....	....	....	+	+	....	1 mo.	5 hrs. 3 applications.	No reaction....	No reaction.....	No reaction.....	No reaction....	No reaction.	Little change
												Same .....	Blister, flush not so wide.	Reaction a little less acute.	Same .....	Subsiding; no difference.	
												Same .....	5 hrs. Slight reddening around area.	Definite blister.	Slight reddening and swelling.	51 hrs. Fading flush, less swelling.	
												Same .....		Blister broken.			

3. MISCELLANEOUS CONDITIONS.

Name.	Age.	Sex.	Condition.	Anæsthesia.						Plaster applied.	Location of plaster.	Duration.	On removal.	24 hrs. —.	24 hrs. +.	48 hrs. +.	72 hrs.
				Complete.			Partial.										
				Pain.	Temp.	Touch.	Pain.	Temp.	Touch.								
A. K. J. Med. No. 32196	18	F.	Hysteria and psychoneurosis. Onset Dec., 1913. Anæsthesia over rt. forearm, rt. lower leg, and about left knee. Left arm normal.	+	+	....	....	....	+	3 mos.	A. A. Radial surface of rt. forearm. N. A. Radial surface of left forearm.	2½ hrs. .....	Faint flush..... Same .....	6 hrs. Slight flush and faint swelling. Same .....	24 hrs. Blister. Small area of flushing. Same.....	Reaction diminished. Same.....	Area healed. Same.
L. Mc. D. Med. No. 32481	25	F.	Anæsthesia over rt. arm. Sudden onset. Hysterical.	+	+	+	....	....	....	5½ mos.	A. A. Flexor surface of rt. forearm. N. A. Flexor surface of left forearm.	4¼ hrs. .....	Slight flush and blister without serum. Wide zone of flushing. Blister with serum	9 hrs. Blistering over ¾ of area with ft. injection. Large blister. Zone of injection and swelling.	Scaly edge; faint injection. Definite swelling and injection around area (subsiding).	Faint reaction. Some swelling about area.	Scaly pigmented area. Small scab with induration. Faint flush.
W. H. G. Med. No. 32957	49	M.	Tabes. Impaired sensation over III to V thoracic segments.	....	....	....	+	+	+	....	A. A. Just to left of left nipple. N. A. In same line over second rib.	4 hrs. .....	Moist base. No injection. Same .....	3 hrs. Small blister. Wide zone of flushing. No blister. Slight flushing.	Large blister. Zone of inject'n. Slight swelling. Small distended blister. Some around swelling.	Blister. Very slight induration. Slight flush around border of area.	Faint flush.
L. W. Med. No. 32141	27	M.	Cardiac case. Sodium salicylate each day 51 from Feb. 16 to Mar. 1. Sensation normal.	0	0	0	0	0	0	....	Flexor surface of each arm.	3 hrs, .....	Slight injection	6½ hrs. Blister. Definite flush.	Definite flush. Slight swelling.	Reaction diminished.	Faint flush.



the plasters. We do not believe, therefore that, where definite inflammatory reactions are obtained in both the anæsthetic and normal areas, much importance should be attached to slight variations in the intensity of the reactions.

#### SUMMARY OF CHARTS.

(a) There are nine cases in which there was anæsthesia due to injury of the peripheral nerves. In Cases 2, 4, and 8 no reactions were obtained in either the sensitive or anæsthetic areas. In all of the other cases, inflammatory reactions were obtained in both the anæsthetic and control areas. In Cases 1, 5, 6, and 9, the reaction seemed to be slightly less in the anæsthetic areas. However, it should be noted that in Cases 1, 5, and 6, the plasters were not placed on corresponding points of the body. In Case 3 there was more reaction in the anæsthetic than in the control area. In case 7 the reaction was practically the same in both areas.

(b) There are four cases in which there was anæsthesia due to lesions of the central nervous system, three of which (Cases 1, 2, 4) showed partial anæsthesia, and one (Case 3) complete anæsthesia. In Case 1, the reaction was a little greater in the control area. In Case 2, the reactions were identical. In Case 3, the reaction was more intense in the anæsthetic area. Case 4 gave no reaction in the anæsthetic area, although three applications were made, whereas control areas on this patient's wrist and on the ankle of another patient gave definite inflammatory reactions in a shorter time.

(c) Of the hysterical anæsthesias one gave identical reactions, and in the other the reaction was less in the anæsthetic area. In the tabetic case the reaction was a little greater in the area of impaired sensation. In the sodium salicylate case the reaction was apparently normal.

#### DISCUSSION.

In the cases of subgroup (a) the inflammatory reactions in the anæsthetic and the control areas varied greatly. In some cases they were identical, in some the reaction was greater in the anæsthetic area, while in others it was less. This result seems to be opposed to the theory of Bruce, for in all the cases

the anæsthetic areas were apparently free from sensory nerve endings, and yet an inflammatory reaction to the irritant resulted. It is true that the reaction was in some cases suppressed in this area but, inasmuch as this finding was not constant, no importance can be attached to it. Subgroup (b) contains the only case in which no inflammatory reaction in the anæsthetic area was obtained when the control areas showed a well-marked reaction. In this instance we were dealing with an anæsthesia due to pressure on the thoracic portion of the cord by a tumor. That the peripheral nerves were not degenerated in the anæsthetic area is shown by the fact that sensation and function soon returned after treatment of the tumor with radium.

#### CONCLUSIONS.

1. With the sensory nerve endings eliminated by degeneration an inflammatory reaction is produced with mustard seed oil, which is identical with that shown in the control while it lasts, but which subsides more rapidly than in the control and returns more quickly to normal.

2. Cantharides plaster produces inflammation in anæsthetic areas in which the sensory nerve endings have degenerated. This reaction is identical with that observed in the control areas.

3. In areas in which local anæsthesia is produced with alypin a definite inflammatory reaction is produced by mustard seed oil.

4. Morphin and chloral modify the inflammatory reaction to mustard seed oil in the eye, but probably not through their action upon the sensory nerve endings.

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## NOTE ON THE OCCURRENCE OF *BACTERIUM WELCHII* (*BACILLUS AEROGENES CAPSULATUS*) IN THE DEJECTA OF CHILDREN.

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During the past few years numerous observers have ascribed an etiological significance to the abnormal development of *B. aërogenes capsulatus* in the intestinal tract in a variety of pathological conditions. This trend of investigation apparently had its origin in the work of Herter,<sup>1</sup> who maintained that the "gas bacillus" is a causative factor in pernicious anæmia and is more abundant in the dejecta of those suffering from this disease than in normal individuals. As a result of its development, an abnormal putrefaction occurs in the intestine and the absorption of various toxic products gives rise to the

pathological condition. At the same time Herter claimed that this species is more frequently encountered in the dejecta of adults and of people advancing in years, than in the young. The remarkable properties of *Bacterium welchii*, particularly its power to decompose carbohydrate and protein materials with the elaboration of important putrefactive products, has lent some plausibility to the views of Herter.

Recently Kendall<sup>2</sup> and his co-workers have advocated the rôle of the "gas bacillus" in the causation of certain types of summer diarrhœa in children, where there seems to be chemical



evidence of extensive putrefactive decomposition. In view of the observations of Herter and Kendall, it becomes a point of some importance to determine just how frequently *B. aërogenes capsulatus* can be isolated from the normal individual. Its wide distribution in nature, especially in soil, milk and water, would render it probable that this organism exists constantly in the intestinal contents; while the frequency with which it is associated with surgical injuries, where the skin is involved, indicates that it finds a ready accessibility to the surface of the body. We have, therefore, made an examination of the dejecta of a number of children in the Harriet Lane Home to determine this point. These children varied in age from two to twelve years, and were admitted to the home for a variety of ailments. In no case, however, were there any evidences of dysentery, and these cases may properly be classified as normal in so far as the intestinal tract was concerned. At the same time the stools of several babies in the obstetrical ward were also examined for the "gas bacillus." The classical methods in vogue for the isolation of the organisms were employed in all instances. A number of tubes of litmus milk were inoculated with portions of the dejecta, heated to 80°-85° C. for 30 minutes, incubated anaërobically and examined after 24-48 hours for the reaction characteristic of Welch's bacillus; namely, acidification and coagulation of the casein, retraction of the curd and evolution of gas bubbles with an odor of butyric acid, the so-called "stormy fermentation." It should be noted here that *B. aërogenes capsulatus* does not liquefy casein and the typical "gas bacillus" reaction consists of a retraction and shrinking of the curd without liquefaction. Whenever any of the inoculated milk tubes showed the typical reaction, rabbits, after being inoculated with small quantities of whey (lcc.), were killed and kept in a warm place for the development of the characteristic gaseous decomposition of the tissues. Finally anaërobic cultures were prepared from the animals and an attempt was made to obtain the organism in pure culture. Only when the milk tubes were positive, the rabbits revealed characteristic lesions, and the organism was obtained subsequently on culture, was the diagnosis of "gas bacillus" regarded as established. The combination of aërobic spore-bearing bacteria capable of growing anaërobically and gas-producing anaërobes often produces a reaction in milk strikingly like that due to *B. aërogenes capsulatus*. The diagnosis of "gas bacillus" is hardly justified, therefore, without the production of characteristic lesions in rabbits and the

isolation of the organism from the tissues. Our results may be summarized as follows:

In 18 children suffering from minor ailments but without marked derangement of the intestinal tract *B. aërogenes capsulatus* was isolated on the first examination in 9 cases. The original milk tubes showed characteristic reactions, the rabbits revealed gaseous œdema on inoculation and positive cultures were obtained from the organs and tissues. In nine other cases the organism was not obtained on the first trial, but subsequent examination revealed it in all instances. In some of the cases the majority of the milk tubes inoculated had a characteristic appearance at the end of 24-48 hours. In 2 cases the first examination was negative, but material was not available for a second trial. In 7 breast-fed infants from the obstetrical ward the dejecta from 6 were negative for the "gas bacillus" reaction, although 15 to 20 tubes were inoculated with material from each case. In one instance, however, one milk tube in the series inoculated gave positive results. In this case the possibility of contamination can not be excluded. It is evident from the results of this inquiry that *B. aërogenes capsulatus* must be regarded as a normal and constant inhabitant of the intestinal tract in children except in breast-fed infants. Similar results have recently been obtained by Orton<sup>3</sup> at the Worcester State Hospital. The attaching of any pathological significance to the presence of this species in the intestine can, therefore, properly be made only when evidence can also be adduced to show its excessive development. In view of the fact that in several of our normal cases the majority of the milk tubes gave positive results, we are of the opinion that satisfactory evidence of an abnormal proliferation of the species in pathological cases has not thus far been brought.

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## NOTES AND NEWS.

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## PROCEEDINGS OF SOCIETIES.

### THE JOHNS HOPKINS HOSPITAL MEDICAL SOCIETY.

OCTOBER 19, 1914.

The meeting was called to order by the president, Dr. John Howland. The election of officers for the ensuing year was then held. Dr. W. S. Thayer was elected President and Dr. W. A. Baetjer, Secretary.

#### 1. Presentation of Cases.

#### 2. Animal Calorimetry. DR. GRAHAM LUSK, Cornell Medical School.

This paper appears in full in the current issue of the BULLETIN.

NOVEMBER 2, 1914.

#### Experiments on the Attempted Transmission of Leukæmia to Monkeys. DRs. A. W. SELLARDS and W. A. BAETJER.

Dr. Baetjer reported the results of experiments made by Dr. Sellards and himself in the attempt to transmit human leukæmia to lower animals.

He spoke of the diversity in the clinical manifestations, of the difficulties in the diagnosis of the acute leukæmias, and of the present views regarding the relation of the acute and chronic forms. The dispute as to the nature of the disease, whether of infectious or neoplastic origin, was considered and the arguments advanced by the adherents of both views were enumerated. It seemed to the authors that more substantial arguments could be advanced in favor of the infectious theory, and that the experiments reported herewith tended to support this view. The various organisms which have been cultivated both from the blood during the terminal stages of the disease and from the viscera at autopsy were reviewed, as well as the numerous previous attempts at transmission of the disease to lower animals. All of these attempts have so far been unsuccessful. Various other methods of attacking the problem suggested themselves, but the one which seemed most promising was the use of the spleen as the site of injection (in spite of the many obvious arguments which might be advanced against it).

The following results were produced in animals inoculated with an emulsion of spleen from a patient dead from acute leukæmia. The history was one of rather sudden onset in a young, robust



adult, who had previously had no serious illness of any kind. There was no history of any recent infection. The disease manifested itself chiefly by fever, tachycardia, a slight icteroid tint to the skin and conjunctivæ, and a rapidly progressing anæmia. The physical examination was practically negative; blood cultures negative; leucocytes 18,000 to 20,000. The stained smears showed the blood picture of acute leukæmia. The disease ran an acutely fatal course. The autopsy showed only parenchymatous changes in the epithelial organs, a few old infarcts in the kidneys and a moderate enlargement of the spleen suggesting an acute splenic tumor of moderate degree. Unfortunately, an examination of the bone marrow was not permitted.

The entire spleen was removed as aseptically as possible. Large areas of the surface were thoroughly seared and deep wedges of tissue removed through this seared area. Cultures made on various media with bits of tissue from the deepest portions of the wedges (*i. e.*, as far as possible from the surface of the organ) all remained sterile. An emulsion of this tissue was then made in physiological salt solution and used for the injections into animals.

The first animal—a monkey—died during the injection, although the amount used was much less than had been given in many previous similar experiments. A half-grown cat was then injected with similar material. There was no shock, the wound healed and for two or three days the cat seemed quite normal. About the third day, it began to get sick, refused to eat, emaciated very rapidly, went into a condition of coma and died on the sixth day. About six hours before death, smears made from the ear showed a very curious condition of almost complete aleukæmia. There was no sign of infection, the peritoneum was perfectly clean and we were rather at a loss to explain the death, except on the basis that we were dealing with some severe and powerful toxic substance. The spleen of this animal was made into an emulsion and injected into a second cat. The animal ran through a course almost identical with that of the first, and also died with almost complete aleukæmia. From the second cat we divided the emulsion of spleen into two parts and injected one into a third cat and the other into a monkey. In this last cat, the technique was apparently not good, as the wound broke down and the cat died in a few days of general peritonitis. The monkey was apparently quite well for a week or ten days and showed no evidence at all of shock. Before operation the animal's spleen was just palpable and the white blood count was 25,000. The operation took place on February 16. On the 21st, the leucocytes had fallen to 13,000. On the 25th, the count had again risen to 25,000, or about normal for the monkey. No examinations were made from February 25 to March 10. A count then showed that the leucocytes had jumped from 25,000 to 54,000, and the animal had become sick. He was weak, easily handled and his spleen had enlarged to about four times the normal size. The differential count at this time showed 18% of polynuclear cells and 82% of mononuclears against his normal rates of 40% of polynuclears and 60% of mononuclears. Stained smears showed a number of pathological cells, both myelocytes and myeloblasts. On the 13th the condition was about the same. The spleen showed no tendency to decrease, was freely movable and apparently not tender. The white blood cells had risen to 56,000. Two days later, we were astonished to find the count had fallen from 56,000 to 26,000, although there was no change in the clinical picture. The explanation of this was apparent on examination of smears made on the 13th, which showed enormous numbers of disintegrating cells, although special precautions had been taken in these examinations to avoid trauma. On the 18th it seemed that the animal was getting better, and it was decided to remove a portion of the spleen for culture, stains and reinoculations. Cultures made anaerobically and aerobically on various media from the quarter of the spleen removed at this time remained sterile. Stained specimens showed

no organisms whatever. From March 20 to April 4, the condition fluctuated. On the 16th we decided to operate again and removed half of the remaining spleen. At the present time the animal has more spleen than normal.

Two features remain to be explained. A blood culture, taken at autopsy of the first cat, grew a micrococcus after about three weeks incubation. Moreover, the original spleen from the patient, after standing for ten days, also showed a micrococcus in cultures made at this time. We feel, however, that these organisms could not in any way have been responsible for the changes produced in our animals for the following reasons:

1. In the first cat (from whose blood the organism was grown at autopsy) much of the same material used in the splenic injection was put also into the peritoneal cavity; yet there was no sign of infection at autopsy. The culture took several weeks to grow out, which would indicate that very few organisms were present and in addition the organisms may well have been terminal invaders. More striking than this, however, is the fact that all of the blood obtainable, as well as the bone marrow from two of the long bones of this cat, was injected into the spleen of another cat without effect.

2. In regard to the organisms cultivated from the original spleen of the patient after it had stood for ten days, two controls were made. The day after the organism was grown, an emulsion of this spleen, similar to that used in the first experiments was injected into the spleen of another cat. This animal remained well and showed no changes except a temporary polymorphonuclear leucocytosis. To control this still further, a milk culture of this organism was then injected into the spleen of a normal monkey, as well as subcutaneously. The animal reacted with a leucocytosis of 30,000, and showed 95% of polymorphonuclear cells.

From these controls, therefore, we felt justified in concluding that these two organisms could have had nothing to do with the aleukæmic death of the first two generations of cats, or the subsequent changes produced in the monkey.

We feel consequently, that with an emulsion of spleen from a case of acute leukæmia, we have been able to cause death in aleukæmia in two generations of cats, and that with the emulsion of spleen from the second generation of cats, we have produced in a monkey a blood picture with suggestive, although not typical, leukæmic changes, and also a splenomegaly of about four times the normal size.

The conclusion suggests itself, to us at least, that an abortive transmission of leukæmia has been obtained, which differs in some respects from the typical human picture, perhaps on account of the natural resistance of these animals to this disease.

#### DISCUSSION.

DR. BARKER: I had the pleasure of following these experiments of Doctors Baetjer and Sellards and was much interested in them. The acute leukæmias are much commoner than we used to think them. We discover them now when we did not before, because we suspect their existence and look at the blood in cases where we failed to look formerly. I think the general practitioner ought to keep in mind that a severe stomatitis, with rapidly developing anæmia and hemorrhagic diathesis, is due in a large proportion of cases to acute leukæmia.

As to the relation of acute leukæmia to chronic leukæmia, just a word. It is very rare to see an acute case of leukæmia go over into a chronic one; but chronic cases not so rarely become acute, especially after treatment with the X-ray. A good many of the deaths in chronic leukæmia are instances in which after marked improvement for a time, the patient grows worse and the blood picture takes on, in the exacerbation, all the features of an acute leukæmia.

As to the nature of these acute leukæmias—whether they are lymphadenoid or myelogenous in origin, or both, is much disputed.



Formerly, all the acute leukæmias were supposed to be of lymphadenoid origin. At present the pendulum is swinging and people are beginning to ask if acute myeloid leukæmia is not commoner than the acute lymphatic form. I think it is pretty clear, if we accept Naegeli's criteria for differentiating the several varieties of unripe white cells, that we meet with both forms, though it is likely that acute myeloid leukæmia is the more common. One important point to be kept in mind is the demonstration of the occurrence of a leukæmia of the micromyeloblastic type. The general practitioner cannot be expected to distinguish between the two forms of acute leukæmia; even the most skilled clinical hæmatologist may have difficulty in the differentiation.

The possibility that the leukæmias are neoplastic in nature has often been suggested. There are two facts that favor the view. One is the occurrence of the chloro-leukæmias, in which remarkable tumor formations are met with about the head, especially in the orbit. The other is that in most leukæmias we see extra-myelogenous leukopoietic foci, which are suggestive of actual metastases of bone marrow tissue. That is a very interesting feature of the leukæmias, but it does not necessarily indicate that they are actually neoplastic in origin. Indeed I think the evidence is strongly against a neoplastic basis. What we have to deal with in the leukæmias is the stimulation to growth of a given variety of cell-tissue wherever it exists throughout the body. Thus, in myelogenous leukæmia, we have an over-activity of the myeloid leukopoietic tissue throughout the body, and in lymphatic leukæmia an over-activity of all the lymphadenoid leukopoietic tissue throughout the body. It looks as though we had to deal, in such stimulation to over-activity, with the action of some soluble substance circulating in the blood or in the lymph. Of course, such a soluble substance might have its origin in a parasite, but if so, the remarkable reaction specific for a given tissue widespread in the body, would scarcely be due to the direct effect of the parasite, but rather to its indirect action through the production of a soluble toxin.

It seems to me that these experiments of Doctors Sellards and Baetjer support this idea. Though they are not asserting that they have reproduced the disease, what they did do was to produce a temporary tissue-reaction, which gave rise to a blood picture similar to that which is more permanent in leukæmia.

DR. SCHMEISSER: I have been very much interested in experimental leukæmia for the last two years. In the laboratory we have confined our attention mostly to leukæmia of the fowl, and have succeeded in transmitting the disease to more than 25 animals. We have also been very much interested in human leukæmia. With material of the same we have inoculated several monkeys. Our experiments in the inoculation from the human to the monkey have been negative.

The point of interest in Drs. Baetjer and Sellards' report is whether leukæmia has been transmitted. We agree with Drs. Baetjer and Sellards that the normal white blood count of the monkey is about 25,000. Indeed, we have had as high as 29,000 w. b. c., so the increase to 56,000 would not be so very great. The drop in the polymorphs with an increase in the mononuclear cells of the blood is suggestive. To my mind, the finest proof that the disease has been transmitted is the appearance of the myelocytes and the myeloblasts in the blood. That seems to be the most striking evidence. The enlargement of the spleen is likewise an important factor; but did it show the characteristic leukæmic changes both gross and microscopical? In our fowl leukæmia it is interesting to note that the cases invariably go to death. We have had only one case of spontaneous cure. The monkey in this instance entirely recovered.

Has sufficient evidence, therefore, been presented to accept a transmission of human leukæmia to the monkey?

Dr. Baetjer omitted reporting a very interesting communication that came out in the *Wien. klin. Wchnschr.* for April 10, 1913,

in which Professor Wiczowski tells us that he has transmitted human leukæmia to the fowl. The patient from whom he took his material was a male, 24 years of age, who had glandular enlargement and a white blood count of 590,000. The blood picture was that of pronounced lymphatic leukæmia. Dr. Wiczowski injected pleural exudate intravenously and after an incubation period of six weeks the chicken became sick, showing characteristic pallor of the comb, mucous membranes, etc. The blood picture was pronounced. He feels very strongly that he has communicated the disease, and claims that the blood picture was similar in every respect to the human case from which he took his material.

DR. WELCH: Dr. Barker's comments are extremely interesting and valuable. It is true that the conception of leukæmia as a neoplasm of the bone marrow, is very popular today, and is set forth very attractively by Dr. Mallory in his book on histology. He describes the blood picture as being nothing more than a circulatory metastasis. Dr. Barker I think stated very forcibly the objections to that interpretation of leukæmia.

The conception of leukæmia from the beginning has been very interesting. Of course it was first really described by Hughes Bennett and misinterpreted by him as a suppuration of the blood. Virchow is credited by all Germans with the discovery of the disease, on the ground that Hughes Bennett misinterpreted the findings, but I think he really deserves the credit for the discovery. In giving a complete summary of the literature as to the origin of the work, one must not exclude Löwit's work, who believed that he had found the parasite in the blood. Of course his conclusions have been disproved. That these acute leukæmias are due to changes in the bone marrow was contended even before the conception that so-called acute lymphatic leukæmia was due to homogeneous myelocytes. Recently one author has pointed that out very clearly in a case of acute lymphatic leukæmia in which the lesions were not in the lymphatic glands but in the bone marrow. This seemed to be so contrary to all Ehrlich's ideas that it was regarded by some as a distinct argument against the separation of the two different sorts of leukæmia. I remember speaking with Ehrlich about it and he said: "Why can you not have a leukæmia produced in the bone marrow?"

In the interpretation of Dr. Baetjer's specimens, a great deal depends on the problems of those mononuclear cells. If they are really not myeloblastic in origin, one might hesitate to regard this as a true leukæmia.

#### Experimental Studies in Methods of Typhoid Immunization.

DR. FREDERICK P. GAY, University of California, Berkeley, Cal.

This paper is a summary of work done on typhoid immunization in the University of California Medical Department. The results appear in detail in the *Archives of Internal Medicine*, 1914, XIV.

#### DISCUSSION.

DR. FORD: I don't suppose there is anybody here so thankful for this method of Dr. Gay's as I am. I took the typhoid vaccination last summer and it spoiled my vacation. After the first inoculation I had a temperature I think of 107° F. I passed an absolutely sleepless night and was completely prostrated the next day. It was five o'clock in the afternoon before I felt better. I comforted myself with the thought that as I had had a bad reaction the first time, the second would not be bad. Then I took the second inoculation, which was worse than the first. I thought then I was out of it, but I picked up an intestinal infection which it took me a week to throw off. Finally I did take the last inoculation and did not have any untoward effects from it; but I should say it was nearly a month before I recovered from that inoculation. There were a great many men who had the same sort of reaction. The



vaccine apparently was a pure typhoid vaccine and there is no evidence that any other organisms were present.

If you will read the history of typhoid vaccination over, you will find that untoward effects, sometimes really dangerous, are by no means uncommon. For instance, great prejudice against Wright was roused among the British soldiers by the uncomfortable results of typhoid vaccination. In that connection, I should say that Dr. Gay's work is of the utmost importance. If we are going to use typhoid vaccination in this country, we must have a method which does not produce such extreme discomfort as apparently can be produced at present. Probably you remember that Dr. Osler made the suggestion that the British soldiers should be inoculated against typhoid and the *London Times* said the amount of disability which was produced altogether overbalanced any protection which might be afforded. I am sure if Dr. Osler had known of the work of Dr. Gay, he might have replied that a method had now been established by which the untoward results could be avoided.

DR. HUNNER: Dr. Gay spoke rather positively about the long continued immunity in people who had had definite cases of typhoid. We are asked so often by people who have had typhoid fever: "Shall we have the vaccination again?" I should like that point cleared up.

DR. WOLMAN: In illustrating the skin reaction, is it necessary to use an organism of the same strain as that of which the vaccine is made?

DR. WELCH: It is interesting to note that Dr. Gay has found this use of our typhoid work here. Those experiments were begun here by Dr. Blachstein, and when he left I carried them to completion. We found that we could occasionally produce intestinal lesions, and even ulcerations on the intestine, which seemed to be very encouraging as a reproduction of the picture of typhoid in the human being. We then made controls with the colon bacillus and found we could get the same lesions we had obtained with the typhoid bacillus. We soon went on to other questions, such as the varying virulence, fatal doses, etc. Before he left, however, Dr. Blachstein had marked with aniline dyes the various rabbits used in our experiments. Those of them that had survived the dosage, we concluded had simply recovered, and some of them were used for other experiments. The others were put back into cages in the laboratory. After about four or five months, some of the rabbits Dr. Blachstein had marked began to die, and I made autopsies. At first I supposed the deaths were purely accidental and that they had nothing to do with the previous inoculations. I found, however, what is described in those papers to which Dr. Gay has referred; namely, that the organisms had disappeared from the blood and organs, but that there was a very remarkable condition of the gall-bladder. It was much distended with pale bile and a grumous material, which might seem to be the beginning of a rather friable gall-stone. It can be seen, therefore, that in our cases of intravenous inoculation of small doses of typhoid bacilli or colon bacilli, the dose was short of fatal. We conceived the organism reached the gall-bladder through the chronic foci in the liver, which occur in rabbits after intravenous injection with colon or typhoid bacilli. Whether that interpretation was correct or not, is perhaps an open question, for if the organism produced a necrotic lesion in the liver, then we would surely get the bacilli in the bile. There, more or less withdrawn from active bactericidal substances, they would simply survive indefinitely, but not without injury to the animal.

The formation of these grumous masses in the bile led us immediately to the examination of gall-stones with reference to the presence of bacteria, and we found it was not a very rare occurrence to have bacteria in the interior of gall-stones. This led us to surmise that these gall-stones were the not infrequent result of a cholecystitis.

These rabbit carriers, which we were the first to produce, as used in the experiments which Dr. Gay has made, have interested me immensely.

I should like to ask who supplies the vaccine.

DR. GAY: The California State Board of Health.

DR. WELCH: I have been much impressed with Metchnikoff's work. He entertains the idea that permanent, substantial immunity must come from living organisms. It has been rather a surprise to me on the whole that such good results have been obtained by the use of killed cultures of typhoid bacilli. Of course our striking carriers are examples of the infection with living organisms. In smallpox of course we use living organisms; as in anthrax, rinderpest, etc. This is doubtless perfectly safe, as probably thousands of persons have submitted to the subcutaneous injection for these diseases. However, one would hardly recommend living cultures for these wholesale vaccinations such as are done in typhoid fever.

DR. GAY: The suggestion that the reaction persists at least over long periods of years, might serve to differentiate the histories, as given, of preceding typhoid fever, and perhaps help to straighten out the complex of a history of typhoid in the past with undoubted typhoid in the present. This brings up the question of the existence of former infections of that type, which were not controlled by blood culture methods, or which perhaps date back before the days of blood cultures; all of which undoubtedly leads to present confusion. If the reaction does persist for a long period of time and is absolutely specific, it might be possible to have an alternate for the types of paratyphoid, and so control these conflicting histories.

DR. WELCH: I suspect the statement that second attacks of typhoid fever cannot occur is a pretty strong one, although Dr. Gay's suggestion that the previous attack may have been paratyphoid or abortive typhoid is interesting. I should not be surprised, however, if in ransacking the literature it might not be possible to find examples of the diagnosis with the typhoid bacillus in subsequent cases. I agree that the immunity is a very substantial one.

DR. GAY: In reply to Dr. Hunner, I do not think there is any indication for people who have had typhoid fever. I would suggest trying the skin reaction.

We have tried a number of paratyphoid tests, and I believe one can differentiate between previous typhoid and infections with *B. paratyphosus Alpha*, but not *Beta*. We had one case where we knew the patient had had such an infection, and the isolation of the organism gave a very clear cut reaction.

NOVEMBER 16, 1914.

Exhibition of Cases. Case I.\* DR. A. L. BLOOMFIELD.

The patient, P. K., æt. 32, was admitted on the medical service on October 5, 1914, complaining of stomach trouble. Family history unimportant. Patient's general health has always been good. No history of dysentery. Has been in this country for about 15 years. Occupation, cigar maker. Present illness began September, 1914, about one month before admission, with an acute stomach upset, followed by fever and malaise. No sharp pain, but sweats at night. Cramps in upper abdomen. On examination patient looked pale and sick. Positive findings were dullness at right lung base behind, coarse rales at both bases, and some tenderness and resistance over upper right rectus. Liver and spleen not felt. Leucocytes 20,000. Intermittent fever varying from 98° to 102°. Urine negative. Wassermann negative. Calmette test negative. Blood culture negative. On October 11, liver dullness was 7.5 cm.

\*This case will be reported in full later.



below costal margin. The impression was a probable subdiaphragmatic abscess.

On October 19, exploratory aspiration. 5 cc. of foul pus withdrawn. Transferred to surgical service. October 20, operation by Dr. McClure: drainage of large liver abscess in upper right lobe. Rapid fall of fever after release of pus. Discharged November 16, having gained 16 pounds. A small sinus is still draining.

Bacteriological examination. From the pus aspirated from the abscess, a streptothrix was grown in pure culture. The same organism was subsequently found in the sputum. The patient's serum gave a positive complement fixation test, using this streptothrix as an antigen.

#### Exhibition of Cases. Case II. DR. F. G. EVANS.

The patient, male, colored, laborer, 44 years old, came into the hospital the latter part of September, complaining of pain in the left arm and shoulder and on the left side. Family history points very definitely to lues, but there is nothing in the personal history to indicate an infection. Present illness began two months before admission with pain in left arm and shoulder, with paralysis of the left arm in some of the attacks, also spasms of the latissimus dorsi. On admission, physical examination showed irregular and unequal pupils, both epitrochlear glands palpable and a pulsating tumor in the left interscapular region over which the heart sounds could be heard, an enlarged heart with systolic murmur and radial pulses which were irregular in size and time in relation to each other. Wassermann positive. Diagnosis was an aneurism of the thoracic aorta. Fluoroscopic examination confirmed this. The tumor could be seen increasing in size from day to day.

On October 22, patient was transferred to the surgical service and on the 23d wiring was done by Dr. Finney under local anæsthesia. The course of the disease since then has been somewhat varied. A note, made on November 14, records that the size of the tumor had not decreased, amount of pulsation about the same and no improvement in subjective symptoms.

In contrast with this patient in whom the signs were so marked, I should like to present Case III, miner, æt. 38, from West Virginia, with negative family history. Personal history is of passing interest in that he had had typhus fever and cholera in Poland. Present illness began last December with what he believed to be cold in the side. He was confined to bed until May 1, principally with pain in the back radiating to the epigastrium and being localized in that region. He described the pain as though someone were "sticking a knife into the epigastrium and turning it round." Worked for a few days last summer, followed by several weeks of incapacity. Came to this hospital the latter part of October. Physical examination was negative except that the spine was tender from the mid-thoracic region to the sacral region. Pressure over the 6th and 7th thoracic spines gave pain in the region of the xiphoid. Wassermann negative. Blood picture negative. No increase in blood pressure. Stomach contents normal. X-ray of the spine showed some lipping, but apparently not enough to account for the symptoms. Calmette negative. Urine negative. Temperature normal, pulse about 70. Spinal fluid negative.

Early on first admission, potassium iodide was administered and continued. The improvement was so marked that patient was discharged on October 17. A spinal puncture was done on the Thursday before discharge, and on Friday the patient was up and around with no discomfort. On Saturday night, while in the city, he was seized with severe headache, and was readmitted the following Friday, eight days after lumbar puncture, with a severe headache which lasted for ten days longer. He was entirely comfortable when flat on his back, as is usual with these lumbar puncture cases. He gradually got better, and with the improvement the old pain commenced to return. The paroxysms were very severe and were only controlled by morphia. Potassium iodide

was again started. Physical examination showed no more than on the first admission and the laboratory tests were still negative. Early in November, at the suggestion of Dr. Clough, a fluoroscopic examination was made, and Dr. Waters diagnosed a large aneurism of the thoracic aorta, at the level of the 6th and 7th thoracic spines. After the diagnosis was made, slight but distinct impairment of the percussion note was made out over the level of the 6th and 7th thoracic spines. In this case, with a definite aneurism, there were no signs at all. During the last few days, he has had some sweating of the right side of his face and slight transient dilatation of the right pupil not noticed before. Relatively comfortable at present. Potassium iodide has been continued. Relief has been coincident with the administration of moderate doses of this drug.

#### Studies in Liver Function. L. G. ROWNTREE, M. D., and E. K. MARSHALL, PH. D.

This paper appeared in full in the *Journal of the American Medical Association*, October 31, 1914, LXIII, 1533.

#### THE JOHNS HOPKINS HOSPITAL HISTORICAL CLUB.

NOVEMBER 9, 1914.

The meeting was called to order by the president, Dr. Henry M. Thomas. The election of officers for the ensuing year then took place and Dr. Henry M. Thomas was re-elected president, and Dr. Thomas R. Boggs was re-elected secretary.

#### Beginnings of Medicine in the Middle West. By DR. OTTO JUETTNER, Cincinnati, Ohio.

Dr. Juettner's paper will be published in full in a forthcoming number of the BULLETIN.

#### DISCUSSION.

DR. FORD: I have been much interested in Dr. Juettner's account. Apparently he does not give any credit to Northern Ohio for the development of medical education or medical thought in the early part of the last century. This is entirely justifiable up to about 1843, when a medical college was established in Cleveland some two years earlier than the medical department of the University of Michigan. I have been especially interested because a relative of mine was one of the old-fashioned practitioners in Northern Ohio. He was born in 1813 and when he was eighteen began his medical education by apprenticing himself to old Dr. Peter Allen, the grandfather of the surgeon in Cleveland today. The four years' education consisted in taking care of Dr. Allen's garden and horses, compounding drugs, and taking long drives with him into the country. At the end of the four years he began to practice medicine. He did this without a diploma for ten years, married, raised children and was successful. Finally, however, he was compelled by the increasing knowledge of his deficiencies to seek some outlet, and he went to Cincinnati. Here he fell under Dr. Drake's influence, attending his lectures. He spent most of his spare time the rest of his life eulogizing Dr. Drake.

Dr. Drake was a very religious man and a very well known hymn writer. Some of his hymns have been incorporated into the Book of Hymns of the Presbyterian Church and are very beautiful.

Medical education in Northern Ohio only woke up with the establishment of the medical school in Cleveland. This school has had a very checkered career. At no time were men produced who could be compared with the men in Southern Ohio, with the possible exception of Dr. Gustave C. Weber, prominent about 1850.

I thought it might be worth while to bring Dr. Drake's book on Epidemic Cholera, which next to his Diseases in the Interior Valley is his most important contribution. It was issued in 1832, about the time that cholera broke out in Montreal, and is extremely interesting. He seems to incline strongly to the belief that cholera



is a disease which is spread by infectious material from person to person.

DR. GARRISON: I am sure that all must appreciate this eloquent address of Dr. Juettner, and especially the illustrations, which have been so carefully selected. We do not always find pictures so good as these accompanying a historical paper. I know very little about many of the men he refers to, beyond a casual acquaintance with their names and some of the things they did, but the figure of Drake is one which will always have an immense interest in connection with the history of the West. There are one or two Western men, of the type of Drake, who did gigantic work, not only for science, but for the general uplift of the country and the development of its material resources. Such was Powell, of the Geological Survey, who did so much for his own science, for the knowledge of the mineral resources of the great West, and for the development of American ethnology. In the memoir of Powell, published by the National Academy of Sciences, we get the impression of a man entirely self-taught in his special avocations, a natural explorer and investigator, a man who is said to have had no special knowledge of geological memoirs, or of quotations from European sources, whose work eccentric in some respects, no doubt, was certainly characteristic of the Western pioneer. Drake was undoubtedly of this type. He had, as the French say, *pas de chance*, a self-taught, self-helping, self-reliant spirit, who devoted years of travel and expensive investigation to produce the remarkable work which Dr. Juettner has described. The size of this work, two huge volumes covering 1863 pages, alone prevents its exhibition here. I should like to say the same thing about Dr. Juettner's own book on Drake, which, if printed in royal octavo size instead of large quarto, would be of similar dimensions. It is undoubtedly the best history of medicine in the Middle West, a credit to its author, and certainly worth reading. We have a particular interest in Dr. Drake, on account of Billings, who resembled him in originality and versatility, and who was the first after Stillé, I think, to call attention to the merits of Drake's work, in his essay on A Century of American Medicine. As Dr. Welch pointed out, at the Billings's Memorial Meeting, this essay, with its somewhat austere survey of our medical literature in the year 1876, did much to improve the status of this literature by its strictures upon the uncritical, irresponsible writing of the period. The only passage in this somewhat cold-blooded estimate of American medicine, which can be styled eloquent, is the one referring to Drake. Billings was a Westerner of the type of Drake, a man who educated and developed himself, and who owed what he attained and acquired to himself alone. I have here one of the smaller productions of Billings, which probably none of you have seen before, and which is a sort of supplement to Drake's work on the Diseases of the Mississippi Valley. It proposes a sanitary survey of the entire United States, consisting of more than 400 questions, relating to the sanitary aspects and the causes of disease in a given community. Dr. Billings's idea was that if these questions could be answered by the sanitary authorities of the different cities and communities of the country, it would be possible to set in motion the machinery for a perfect system of sanitation. Drake triangulated the interior valley of North America as to its diseases. Billings proposed to blue-print the whole country as to its hygienic requirements. The plan was tried out in two or three cities, but the questions were so difficult to answer, that physicians could not give the necessary amount of time to the matter, while the only alternative, that of employing experts to answer the questions, would have been too expensive. So the proposition was abandoned, but, if carried out, it would have been a justification of Drake's work, and the plan itself is an equally remarkable production of "mind."

DR. WELCH: I can only add a word to what Dr. Garrison has said in appreciation of Dr. Juettner's coming here and giving us this very interesting sketch of the physicians who built up med-

icine in the Middle West. Of course it is very difficult for us to have a standard of measurement in our estimates of physicians of that period. It is well worth while of course, to rescue the local annals of medicine in any part of the country. The interest in the names, however, is rather antiquarian and can hardly make a wide appeal. Even when we estimate the achievements of men in our own country, we have to compare them with their contemporaries elsewhere; and when we attempt to place them in any rank in the world's history of medicine with their contemporaries, that is an entirely different standard. When we consider who were the contemporaries in the first third of the 19th century of these names that we call, from our American point of view, our heroes, of course they play a pretty small part in the universal history of medicine. They were the contemporaries of Astley Cooper, Bichat, Laennec, Rokitansky, etc., and, who were they in that company, you may ask. Some of them, however, have a responsible position in the world's history—three at least: Benjamin Rush, Nathan Smith and Daniel Drake. McDowell, of course, has some claim for his great achievement, but by and large Drake's is the greater name. Benjamin Rush ranks with the systemists of the 18th century. At that time he was the only product of American medicine in that class. His actual contributions were not considerable. Nathan Smith is a not less important figure, but much more modern than Benjamin Rush. We can read now Nathan Smith's paper on "typhus" fever, as he called it, and see how far he was in advance of his day. Benjamin Rush made no such contributions as Nathan Smith, but still he is a great figure. Daniel Drake is I think, and have always thought, the most distinctive product of American medicine, if you emphasize the word American. He is racy and of the soil. He was not trained abroad. As has been set forth, his training was obtained from the medical facilities in this country, the best to be had to be sure, but still relatively meagre. He had, of course, inherent qualities of mind and of character, and when we speak of inadequate education, Did not those men, after all, in the frontier settlements have splendid training out in the woods and with nature? Did they not acquire a kind of resourcefulness which was admirable for their future work as physicians? At any rate this work on the Diseases of the Interior Valley is one of the great contributions of American medicine to medicine. Read what Hirsch says about it, and the references which he makes to Daniel Drake in his great work on Geographical Medicine, and you will see that Drake has decidedly found his place in medicine. So that looked at from the highest, broadest point of view, Daniel Drake does take a very respectable position in the world's medicine.

Many of these frontier doctors were fully the equals in education of their contemporaries along the Atlantic seaboard: in Boston, New York, Philadelphia and Charleston. Of course in the middle of the 18th century, Charleston was perhaps the most cultivated center. There is a wonderful group here that has never been presented to us. I have made many appeals to have this done, by some one from that region if possible. As I said, many of these frontier men were highly trained. McDowell went abroad and studied in Edinburgh, where he was a favorite pupil of John Bell. Bell was an extra-mural teacher, it being impossible to get a University position in Edinburgh in the days of the three Munros, and Bell I think was in the time of the second Munro. However, he was a great surgeon in Edinburgh. Benjamin Dudley's name has great renown, particularly to Kentucky doctors. Ask any one of them and I think you will find that Benjamin Dudley was the greatest human being ever created. Drake's is undoubtedly the greater name, but Dudley was a great personal force there. He lived much longer than Drake. I have talked with the McCormicks and other men from Kentucky and I think they put Dudley on a pinnacle by himself. He had four years' study in Paris and in London, where he was a pupil of Astley Cooper and of Abernethy. Consequently, it is not fair to say those men were not the equals



of their contemporaries on the Atlantic seaboard. I think it is fair to regard Nathan Smith as a pioneer physician, because New Hampshire and Vermont in those days were just as much pioneer settlements as Kentucky and the Ohio Valley. Altogether it was an interesting group of men who flourished at that time in the pioneer settlements of this country, and I am sure Dr. Juettner's studies of this subject are a valuable contribution to a much neglected topic—the study of the annals of medicine in our own country. Medical history and all members of the profession in this country undoubtedly owe him a great debt for his studies in this field.

DR. HURD: Is there not danger of over-estimating the importance of educational advantages? I do not think that we have ever had in the United States a man with a better mind or one who used an inferior training with better purpose born within himself, than William Beaumont. He had no special advantages of education and was largely self-taught, but his name in medicine is fully as great as that of any person whom I can now call to mind. Dr. Daniel Brainard, the founder of Rush Medical College in Chicago, is another example. He was the equal in ability, originality and force of any teacher I ever knew.

We owe Dr. Juettner a great debt of obligation for his admirable presentation of these pioneers. We sometimes assume that medicine began in our time, and forget that there were many effective workers who laid the foundations upon which others have since built.

DR. WELCH: One name incidentally mentioned by Dr. Juettner has interested me. It is that of Charles Caldwell. If you want some of the most spicy and interesting reading of those days, get the autobiography of Charles Caldwell. If you can get a copy of this book, I am sure you will enjoy it.

It is not difficult to pick up the two volumes of Drake's Diseases of the Interior Valley. I think they are often seen in second-hand book stores.

DR. JUETTNER: I have but a word of appreciation for the friendly and extremely pleasant reception accorded to my humble efforts.

I wish to say to Dr. Ford that, my reason for not including the features he refers to, is that they belong to a later period. The period of which I speak ended about 1830.

I wish to thank Dr. Welch particularly for the encouragement he has given this line of study, which I see is pursued with some degree of interest here in the East, and which is absolutely ignored and neglected in the West. In my own experience I have found two things: first, nobody knew anything about Daniel Drake, even the men identified with the medical schools; and, second, when this little effort of mine came out, nobody knew who he was. I remember the professor of practice at the Ohio Medical College said, when I showed it to him: "That is a lot of work you did," and finally, shrugging his shoulders: "Cui bono?" I felt, however, that the day would come when such a subject as this would receive the notice of which it was deserving. I thank you for your interest.

## NOTES ON NEW BOOKS.

*Manual of the Diseases of the Eye.* By CHARLES H. MAY, M. D. \$2 net. (New York City: William Wood & Co., 1914.)

May's book has gone through seven editions and is apparently increasing in favor with the profession. We note the second Japanese edition has just been issued.

The manual possesses unmistakable value for the student and is full of practical observations as well as being free of so much that is to be found in larger text-books on the eye, much that is of course interesting but not essential, and which had best be left out of a work which is designed especially for students.

The suggestions as to the treatment of conjunctivitis are excellent, though it seems to the reviewer that too much importance is attached to protargol and argyrol, which latter, by the way, is one of the most emasculated products we have at our command. It is left to the doctor to choose one of these agents, when in our opinion it would be better to use a 1 per cent silver nitrate solution at once and to continue its use as long as there is any exudate. It sometimes seems that the resort to argyrol is simply "fiddling." The reviewer has never seen any ill results follow the use of silver nitrate, and when used in the proper strength it does all that is expected of a silver salt and more effectually than is done by any of the others. As the exudate disappears the substitution of a weak solution of zinc seems advisable. Again, the practical side of this book has not been overrated as has been said more than once in the BULLETIN and we are convinced that the eighth edition is launched upon a useful and successful career.

*Local Anesthesia: Its Scientific Basis and Practical Use.* By PROF. DR. HEINRICH BRAUN, Obermedizinalrat and Director of the Kgl. Hospital at Zwickau, Germany. Translated and edited by PERCY SHIELDS, M. D., A. C. S., Cincinnati, Ohio. From the third revised German edition. With 215 illustrations in black and color. (Lea & Febiger: Philadelphia and New York, 1914.)

The work is based on the clinical and experimental observations made by Prof. Braun during the many years he has been interested in local anesthesia.

Ten of the 16 chapters are devoted to a thorough general exposition of the entire subject of local anesthesia, including the history, methods, drugs used and general technic. In the last six chapters the special technic of local anesthesia for operations on the head, neck, spinal column and bony thorax, abdomen, genito-urinary organs, rectum, and extremities, is considered in detail. The illustrations show the points of insertion and line of infiltration used in the various nerve-blocking operations. They also show the magnitude of operations which can be performed under local anesthesia. No mention is made of quinine and urea as a local anesthetic, and Hohmeier's method of approaching the brachial plexus from below the clavicle is not considered.

The author is to be congratulated on producing a book in which local anesthesia is systematized into a logical procedure, based upon scientific facts and having an exact technic. The possibilities of local anesthesia have not been fully appreciated in this country, and this excellent translation will place in the hands of American surgeons a splendid work on the subject.

*The Tonsils.* By HENRY A. BARNES, M. D. Cloth, \$3. (St. Louis: C. V. Mosby Company, 1914.)

There is much valuable and useful information in this book, particularly in the chapters dealing with the general nature of lymphoid tissue, and the development, anatomy and histology of the tonsil. The section devoted to the relation of the tonsils to systemic infections, however, is disappointing. Coming, as it does, from the clinic of the Massachusetts General Hospital, we had hoped that this book would contain records of their own experiences in regard to the etiological and therapeutic importance of focal lesions in the upper respiratory passages in their relation to general systemic disorders. It is somewhat disappointing, therefore, to find only a brief summary of the observations of Billings, Rosenau and Davis, together with a list of the diseases that "have been attributed" to a primary focus in the tonsils.

The chapter on the surgery of the tonsils contains illustrations of special instruments and of the author's own method of remov-



ing tonsils. He fails, however, to insist on the basic surgical principle of the ligation of the vessels in order to control hemorrhage.

*Effects of Volcanic Action in the Production of Disease and Atmospheric Vicissitudes.* By H. J. JOHNSTON-LAVIS. Cloth, 75 cents. (London: John Bale, Sons and Danielsson, 1914.)

This little volume of less than a hundred pages was the recipient of the Parkin prize of the Royal College of Physicians of Edinburgh, and was prepared by the author upon the special topic set for the competitors. It gives an interesting and apparently authentic account of the various factors concerned in volcanic eruptions and the effect of these eruptions upon the composition of the atmosphere. A number of citations are made which testify to the belief current in early times among the inhabitants of volcanic countries that the effluvia from active volcanoes are harmful to life, the most important of which is a description by a certain Dr. Jean Vivinzio of an epidemic which seemed to follow the eruption of Vesuvius in 1760. As the author indicates, modern knowledge of the etiology of epidemic diseases has proven that most of the epidemics described in early times are to be referred to other causes than volcanic effluvia, while the volcanic eruptions of recent times, the effects of which have been carefully studied, have not been followed by the appearance of disease in epidemic form.

*Dietetics, or Food in Health and Disease.* By WILLIAM TIBBLES, LL. D., M. D. 627 pages. (Philadelphia and New York: Lea & Febiger, 1914.)

Probably no one branch of clinical medicine has been subjected to so much valuable scientific study as that dealing with the laws which govern the diet of healthy and sick individuals. In fact, dietetics has rapidly become a science and one with which every intelligent practitioner must be familiar. The studies of Lillie and Loeb on the various inorganic salts, of Osborne and Mendel on the insufficiency of various proteins, of Casimir Funk and others on the so-called vitamins, of Coleman and Du Bois on the value of a liberal diet in typhoid fever: these are only a few of the epoch-making studies which have advanced the subject of dietetics in recent years. Other work, such as that on the lipoids, amino-acids, and phosphorus deficiency, has done much toward clearing up the etiological rôle which diet may play in certain obscure metabolic diseases.

The aim of this book has been to incorporate all these recent advances, to apply them in practice, where possible, to give the already known dietetic laws due emphasis, to provide a ready source of reference with suggestions for the handling of all conditions in which food may exert a beneficial modifying influence, and finally to stimulate further research. It may, with reason, be said that to accomplish all this within the space of 600 pages is a well-nigh impossible task, but the author has accomplished it with unusual clearness, accuracy and judgment. Moreover, the book is replete with the evidences of first-hand experiences, and is written with a genuine literary ability not commonly displayed over such a theme. In other words, the book is valuable, practical and readable. It is divided into two parts: the first deals, in eight chapters, with foods, their caloric values, digestibility, absorption and composition. Metabolism in the light of present views is discussed and is followed by chapters on the amount and kind of food required in many circumstances and the feeding of infants and the aged. An excellent chapter deals with special types of diets, such as vegetarianism, fruit cures, meat diets, zomotherapy, nitrogen, purin, fat and salt free diets, etc. Part 2 is concerned with the dietetic treatment in various forms of disease: under

each, several types of diet are presented together with concise statements of the views held by other eminent authorities. Throughout the book there are numerous and invaluable tables, and frequent footnote references to the literature. The closing chapter on vitamins and the deficiency diseases is particularly well done. All things considered, the book is probably the best thus far published on the subject.

*Serology of Nervous and Mental Diseases.* By D. M. KAPLAN, M. D., Director of Clinical and Research Laboratories of the Neurological Institute, New York City. Octavo, 346 pages, illustrated. Cloth, \$3.50 net. (Philadelphia and London: W. B. Saunders Company, 1914.)

The singular lack of any American work covering the subject of the serology of nervous and mental diseases induced the author to write the present volume, designed particularly to meet the queries of neurologists and psychiatrists. The first 60 pages are devoted to the history and technic of lumbar puncture, the methods for examining the cerebrospinal fluid, and the various essential steps in the performance of the Wassermann reaction, especially the proper standardization of the various reagents. The author's remarks on the attitude of the serologist deserve careful study. The second section, in some 40 pages, carries one over the serology of nervous and mental diseases of non-luetic etiology. Then follows a well organized and unbiased statement of the commonly accepted, and the author's own findings in tabes dorsalis, cerebrospinal lues and general paresis. The numerous variations which the spinal fluid may show in all these conditions before and after treatment are well emphasized. Attention is drawn to the apparent value of the colloidal gold test, especially in paresis. The last section deals somewhat in detail with the therapeutic use of salvarsan. Thirty-eight pages are devoted to a tabulation of the best articles in the literature which bear upon the subjects previously discussed. The arrangement of this section might well be improved upon.

Singularly clear and well arranged, this book is certain to meet the needs of those whose work is along lines similar to that of the author. It is free from any serious errors, is fairly well illustrated and is frankly to be recommended as the most valuable treatise of its kind thus far published in the English language.

## BOOKS RECEIVED.

*A Text-Book of the Diseases of the Nose and Throat.* By Jonathan Wright, M. D., and Harmon Smith, M. D. Illustrated with 313 engravings and 14 plates. 1914. 8°. 683 pages. Lea & Febiger, Philadelphia and New York.

*Royal Academy of Medicine in Ireland.* Transactions, Volume XXXII. 1914. Edited by J. Alfred Scott, M. A., M. D., F. R. C. S. I. 8°. 408 pages. John Falconer, Dublin.

*International Clinics.* A Quarterly of Illustrated Clinical Lectures and Especially Prepared Original Articles. By Leading Members of the Medical Profession Throughout the World. Edited by Henry W. Cattell, A. M., M. D. Volume III. Twenty-fourth Series. 1914. 8°. 309 pages. J. B. Lippincott Company, Philadelphia and London.

*Diseases of the Kidneys, Ureters and Bladder.* With Special Reference to the Diseases in Women. By Howard A. Kelly, M. D., LL. D., and Curtis F. Burnam, M. D. With 628 illustrations, for the most part by Max Brödel. Volume I, 582 pages. Volume II, 652 pages. 1914. 8°. D. Appleton & Co., New York and London.



# BULLETIN

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## SOME OBSERVATIONS ON HYPERSENSITIVENESS TO PNEUMOCOCCUS PROTEIN, WITH SPECIAL REFERENCE TO ITS RELATION TO IMMUNITY.

By PAUL W. CLOUGH, M. D.,

*Associate in Medicine, The Johns Hopkins University, and Resident Physician, The Johns Hopkins Hospital.*

*(From the Biological Division of the Medical Clinic of The Johns Hopkins University.)*

The experiments here reported were undertaken in order to determine, if possible, whether or not any constant relation exists between immunity to pneumococcus infection and hypersensitiveness to pneumococcus protein. The relationship of hypersensitiveness to immunity is not yet thoroughly understood. While at first glance the one is apparently the antithesis of the other, there is considerable evidence to show that they are often associated with one another, and that they may represent different manifestations of what is essentially a single process.

The extensive studies of the last 6 years on the reaction of the living body to injections of foreign protein have led to entirely new conceptions concerning immunity from infectious disease. While many of these conceptions were deduced by von Pirquet,<sup>1</sup> as a result of his clinical studies on serum disease and vaccinia, a sound experimental basis for them was first laid by the pioneer researches of Vaughan.<sup>2</sup> The essential features of Vaughan's theory have been embodied and further

elaborated in the interesting theory independently advanced by Friedberger,<sup>3</sup> after a very extensive series of researches. According to this view, bacterial protein, like all foreign protein, is broken up in the circulation into simpler substances by means of specific ferments (Vaughan), or antibodies (amboceptor and complement, Friedberger). In the normal individual these ferments are present in minute amounts, and the rate of decomposition is slow. But as the result of the continued presence of a foreign protein in the circulation, there ensues a specific increase in the amount of the corresponding ferment, or antibody, in the blood. As a result, the foreign protein is broken up much more rapidly than in the normal individual. This increased rapidity of decomposition of the foreign protein may result in immunity, or hypersensitiveness, according to the circumstances in a given case.

The decomposition of the protein is a gradual process, a series of intermediate products being successively formed and broken down into still simpler ones. The native protein itself



is not directly toxic to the body, and the final end products are also quite harmless; but some of the intermediate decomposition products, related probably to peptone, are very poisonous. In the normal animal, the rate of decomposition is so slow that there are not enough of these poisonous intermediate products present at a given time to cause symptoms. In the allergic animal (infected, immunized, or sensitized) the increased rate of decomposition may give rise to the rapid formation of an intoxicating or even of a fatal dose of these poisons, if a large amount of the foreign protein suddenly enters the circulation. The breaking up of the foreign protein is to be regarded as a useful and necessary process; the intoxication as an unfortunate, accidental phenomenon which mars its course. If the foreign protein is one which is incapable of increasing after its introduction into the body, *e. g.*, horse serum, the accelerated decomposition offers no obvious advantage to the individual animal if the dose of the protein is small, whereas it may prove fatal to the animal if the dose is large. The animal is hypersensitive.

On the contrary, if the foreign protein is capable of increase after its entrance into the body, *i. e.*, if it is a living virus, the accelerated reaction usually will be beneficial, since it tends to make possible the rapid and complete destruction of the invading organisms, and thus prevents them from multiplying and giving rise to a fatal infection. The animal is therefore protected, or immune. But this protection depends entirely upon the fact that the quantity of living virus which gains access to the body at a given time, under natural conditions, is usually so small that it cannot yield a dangerous dose of the poison, however rapidly broken up. If the amount of living virus entering the body is large, if for example, it be comparable in amount to the quantity of serum required to intoxicate a sensitized animal, the "immune" animal will be acutely intoxicated, and will succumb much more quickly than a normal animal. The essential nature of the process is identical in the two cases, though it may be disastrous to the individual in one instance, but beneficial in another.

The general symptoms of infectious disease (aside from the action of the true soluble toxins) are attributed by Friedberger to these same poisons, formed as the result of the decomposition of the bacterial protein by specific antibodies (amboceptor and complement). In the normal animal there are no symptoms immediately following infection. The breaking up of the protein by the small amount of normal amboceptor present is too slow to liberate an appreciable dose of toxin. Symptoms appear only after specific antibodies have been formed in sufficient quantity to break up the bacterial protein rapidly. The appearance of symptoms would, therefore, imply the development of a certain degree of immunity.

This view Friedberger has supported by many ingenious experiments. The strongest proof he has advanced is the production *in vitro*, from bacteria, specific immune serum and complement (guinea-pig), of a poison which in large doses causes symptoms in normal guinea-pigs identical with those seen in a fatal anaphylactic reaction. In smaller doses it causes fever or subnormal temperature, according to the dose.

Since the poison causes the same symptoms, from whatever species of organism or foreign protein it is derived, he regards it as a non-specific substance contained in every protein molecule, and has named it anaphylatoxin. The mechanism of its liberation is the only specific feature of the process. This view of the non-specificity of the toxin constitutes the only essential difference between his conception and Pfeiffer's older theory of endotoxines. According to this view of Friedberger, then, the symptoms of infectious disease may be regarded as due to a kind of chronic anaphylactic intoxication.

That a direct relationship or association exists between hypersensitiveness to bacterial protein and immunity to infection is most clearly shown in the case of organisms like *B. typhosus* and *B. coli*. This was indicated by the early work of Rosenau and Anderson,<sup>4</sup> and definitely demonstrated by Vaughan,<sup>5</sup> and others. Vaughan showed that guinea-pigs which had been sensitized by injections of bacterial extracts (colon and typhoid) were definitely more resistant to infection than normal animals.

That a hypersensitiveness to typhoid protein probably develops in man during the course of the disease, along with an immunity, is indicated by the occurrence of ophthalmic and cutaneous reactions (Chantemesse,<sup>6</sup> Austrian<sup>7</sup>).

This theory agrees very well with the facts, when applied to a disease like typhoid. It seems, *a priori*, probable that it would apply to a disease in which the immunity, in large part at least, depends on direct lysis of the bacilli by the serum. But its application is not so obvious in the case of a disease like pneumonia, in which the incubation period is probably very short; and where death in uncomplicated cases is due to a septicæmia, and may occur so early that any noteworthy antibody formation is impossible. Recent studies by Rosenow<sup>8</sup> show that if suspensions of pneumococci in serum or salt solution are incubated at 37° C. for a suitable length of time, toxic substances appear, probably as a result of autolysis, which cause symptoms in normal guinea-pigs identical with those caused by Friedberger's anaphylatoxin. The latter, moreover, may be formed by the application to the organisms of fresh normal guinea-pig serum alone, without immune serum. Friedberger attributes this to the presence of normal amboceptors in the serum. It is, therefore, unlikely that the appearance of symptoms in pneumococcus infections depends on the production of immune bodies.

Nevertheless, it is not improbable that such substances may play a rôle in recovery from the disease. The phenomena at crisis suggest a sudden "deintoxication" of the body. This is certainly not due to true antitoxin formation. It must involve the destruction of the invading micro-organisms, and might adequately be explained, simply by a resulting cessation in toxin formation. The evidence, too, is strongly in favor of the view that this destruction is the result of phagocytosis and intracellular digestion of the organisms. There is no appreciable degree of direct bactericidal or bacteriolytic power to be made out either in normal or pneumonic serum. However, it seemed possible that there might be an increased formation of those ferments, or antibodies, which break up the



pneumococcus protein and its toxic by-products, and that (as suggested by Rosenow<sup>9</sup>) this accelerated destruction of the poison might play a rôle in a deintoxication of the body at the crisis. If so, this might be associated with a demonstrable condition of allergy on the part of patient, and it might be capable of demonstration in properly immunized animals.

With this in view, several series of guinea-pigs were sensitized to extracts of pneumococci, or to killed cultures; while other series were immunized to living cultures. Both the immunity and hypersensitiveness were tested in each series. A pneumococcus protein was also prepared and applied to a series of patients, just as tuberculin is employed in the intracutaneous and ophthalmic tuberculin tests.

The pneumococcus strain used in these tests was isolated from the lung of a fatal case of pneumonia, and was kept at a high stage of virulence by frequent passages through animals. To obtain organisms in large quantity for sensitization work, the strain was cultivated in large flasks of 5 per cent glucose broth, to which finely powdered (not precipitated) calcium carbonate was added. The flasks were shaken occasionally during incubation. After 24 to 36 hours, when the maximum growth was reached, the flasks were shaken up, allowed to stand until the calcium carbonate had settled to the bottom, and the fluid was poured into tubes and centrifugalized. Smears were examined to demonstrate the purity of the culture. The supernatant fluid was decanted completely from the sedimented organisms, and the latter suspended in 50 cc. of sterile salt solution and again centrifugalized. The organisms were thus washed free from peptone and other disturbing constituents of the broth. The washing fluid was decanted completely and the sediment suspended in a few drops of distilled water and dried *in vacuo* over calcium chloride. Unless the desiccation was rapid, the end product was often unfit for use.

The dried residue was weighed and ground for 3 hours in an agate mortar, with a weighed amount of sterile sand, or salt. It was then extracted in salt solution (or in water, if ground in salt) 10 cc. of fluid being used for each gram of dried material. The best results (with this particular strain) were obtained by extracting at 37° C. for 18 hours. The extract was then centrifugalized for several hours at high speed, the fluid being decanted from time to time into a clean tube, till no further sediment was obtained. In some experiments the extract was used at once for sensitization or intoxication of the animals. In others the protein was precipitated from the extract by pouring the latter into 10 volumes of absolute alcohol; the precipitate was collected, dried *in vacuo*, and weighed. The material so obtained is a fine white powder, consisting largely of more or less altered protein. One gram of dried culture residue yields about 0.15 gm. of "protein."

During the process of extraction a considerable degree of autolysis takes place, as already pointed out by Rosenow. As a result the extracts become toxic, and on intravenous injection into normal guinea-pigs cause symptoms identical with those seen in an anaphylactic reaction. Prepared in this way, extracts become somewhat toxic after 18 hours' incubation, and

still more markedly so after 24 to 36 hours. The toxicity is much reduced by heating for 1 hour at 60°, but it is not always entirely destroyed.

TABLE I.—TOXICITY OF EXTRACT FOR NORMAL GUINEA-PIGS ON INTRAVENOUS INJECTION.

No. of animal.	Wt. in gms.	Wt. in gms. of dried culture residue per 250 gms. of guinea-pig.	Time of extraction.	Heated.	Result.
14	250	0.020	18 hrs. 37° C.	Not heated.	0
15	255	0.030	" "	" "	0
5	390	0.040	" "	" "	+ 5 min.
4	275	0.040	" "	1 hr. 55-60° C.	0
6	390	0.040	" "	" "	0
189	340	0.060	" "	" "	+ 3 min.
7	335	0.060	" "	" "	0
9	250	0.060	" "	" "	0
8	325	0.068	" "	" "	0
22	270	0.080	" "	" "	0

Occasional irregularities, such as shown by No. 189, were not rarely encountered. These animals died after showing symptoms characteristic of anaphylactic shock, and showed at autopsy a maximal degree of acute distention of the lungs, as well as numerous subserous hæmorrhages, especially in the pericardium.

Sensitization was carried out by subcutaneous injections of suspensions of killed cultures, or of extracts of such suspensions. The best results were obtained from three injections of 0.02 gm. of dried residue at two-day intervals. Smaller amounts sensitized, but not constantly. An interval of at least 8 weeks was allowed to elapse after the last injection before intoxication was attempted. Sensitization lasted at least from 6 to 8 months.

In all the tests here reported, the injections of extracts made to test primary toxicity, or to intoxicate sensitized animals, were given directly into the jugular vein. The animals were anæsthetized, the vein was dissected out and ligatures were applied. Two to six hours later, after complete recovery, the animal was securely held and the injection made into the vein with a Record syringe, equipped with a fine hypodermic needle. It is quite unnecessary to tie in a canula, but a ligature is often necessary to prevent subsequent bleeding.

Animals which suffered an acute fatal reaction usually showed no symptoms until one or two minutes had elapsed after the injection. They then became restless, and showed rapidly increasing evidences of respiratory distress. After a transient period of accelerated breathing, the respiratory movements became slow, labored, and ineffectual, and it could easily be seen that very little air was entering the lungs. There was deep cyanosis, and often micturition and defecation occurred. Frequently, also, these movements were interrupted by sneezing, or by hiccoughs, which were often associated with spasmodic jumping, or bucking movements. After from three to six minutes, in fatal cases, the animals developed violent general clonic convulsions, which alternated with periods of deep coma. During these periods of coma, there were seen feeble, gasping, respiratory efforts, which became



more and more infrequent and finally ceased at least one to two minutes before the heart stopped beating.

At autopsy the lungs were extremely voluminous, and did not collapse at all when the chest was opened. They were light pink in color, and usually very dry on cross-section. Animals which died after longer intervals and normal animals, which succumbed to the direct toxic action of the extracts, tended to show a less acute degree of emphysema of the lungs, and more congestion and œdema than in the case of animals dying in acute anaphylactic shock. Often the pleural surfaces were mottled with dark purple areas of hæmorrhage. In nearly all cases hæmorrhages were found under the visceral pericardium, varying in size from a pin-point to 5-6 mm. in diameter.

In reactions which were not fatal, the characteristic symptoms were restlessness and respiratory disturbances, followed by weakness and a profound drop in temperature. But as normal control animals also often showed a drop in temperature after doses of extract but little larger than those required to intoxicate a sensitized animal, this symptom was not regarded as a trustworthy criterion of anaphylaxis, in this particular work.

The symptoms described differ somewhat from those characteristic of an anaphylactic reaction to horse serum. In particular one misses the evidences of cutaneous hyperæsthesia. There is only rarely much scratching or biting of the skin, or rubbing of the nose, so often seen in animals reacting to an injection of serum.

The intoxicating power of such extracts of pneumococci for previously sensitized animals is shown in the following table.

TABLE II.—SENSITIZATION WAS COMPLETED NOVEMBER 7, 1912. REINJECTIONS, JANUARY 15 AND 16, 1913.

No. of animal.	Wt. in gms.	Previous treatment.	Wt. in gms. of culture extract per 250 gms. of guinea-pig.	Time of Extraction.	Heated.	Result.	
						Reaction.	Outcome.
8	390	None.	0.040	18 hrs. 37° C.	1 hr. 55-60° C.	0	Lived.
7	335	"	0.060	" "	" "	0	Died in 24 hrs.
8	325	"	0.068	" "	" "	0	Lived.
158	470	Sensitized.	0.030	" "	" "	0	"
157	450	"	0.030	" "	" "	+	Lived ½ hr.
41	250	"	0.040	" "	" "	++	Lived.
154	460	"	0.040	" "	" "	++	+ 5 min.
159	480	"	0.040	" "	" "	++	" "
160	330	"	0.060	" "	" "	++	" "

With suitable extracts it was possible to intoxicate sensitized guinea-pigs with doses that were materially less than those required to produce symptoms in normal control animals. The average dose required to intoxicate a sensitized animal was the extract from 0.040 gm. of dried culture residue for each 250 gms. of body weight. However, the margin between the fatal dose for a sensitized animal and that borne by a normal animal was never very large. There was some variation in the activity of different extracts, and marked variation in the reaction of different individual guinea-pigs to the same extract. It was, therefore, necessary to include several control animals and several treated animals in every test. The rela-

tively large dose of extract required to intoxicate, and the large amount of time and labor required to secure even a small quantity of the extract restricted to an unexpected degree the scope of the experiments.

The various specimens of "protein" obtained by precipitation of such extracts showed still greater variation, both in their primary toxicity, and in their power of exciting true anaphylactic shock. It was necessary to test the antigenic property of each specimen by showing that it would intoxicate sensitized pigs in doses tolerated by normal animals, before using it on man.

The following table shows the properties of a suitable preparation of "protein" after it has been heated one hour at 60° C.

TABLE III.—REINJECTIONS MADE MARCH 29, 1912.

No. of animal.	Wt. in gms.	When sensitized.	Protein injected.	Result.		
				Reaction.	Outcome.	Autopsy.
80	415	Control.	0.040	0	+ 5 hrs.	Negative.
82	422	"	0.020	0	+ 5 hrs.	"
48	400	Dec. 22, 1911.	0.040	+++	+ 3-4 min.	Typical acute distention of the lungs.
24	400	" "	0.020	+++	+ 3-5 min.	Typical.
49	400	" "	0.020	+++	+ 3-5 min.	"
47	400	" "	0.010	+++	+ 3-5 min.	"

Doses smaller than 0.010 gm. gave inconstant results and usually were not acutely fatal. Some preparations of protein, had to be discarded since the dose required fatally to intoxicate a sensitized animal was also fatal to a normal animal.

The precipitated protein possessed sensitizing as well as intoxicating power. A guinea-pig (No. 45) was sensitized Dec. 21, 1911, by a subcutaneous injection of 0.030 gm. of protein. On March 28, 0.020 gm. was reinjected intravenously, and caused a definite anaphylactic reaction, which, however, was not fatal. Two control pigs, receiving intravenous injections of 0.020 and 0.040 gm., respectively, of the same protein, showed no anaphylactic symptoms. Several other guinea-pigs, which had been given injections of 0.03 to 0.04 gm. of protein subcutaneously in order to sensitize them, emaciated and died after 3 or 4 weeks, apparently being poisoned by the injections.

In order to determine whether or not this condition of hypersensitiveness is specific, several series of guinea-pigs were sensitized as above described, (1) to a mixture of several strains of pneumococci, (2) to a single strain of pneumococcus, (3) to a mixture of several strains of *Str. pyogenes*, and (4) to a mixture of several strains of *Str. viridans*. Because of the spontaneous death of some of these guinea-pigs, during the incubation period in which hypersensitiveness was developing, and because some of the extracts did not give constant results, it was not possible to carry out a complete series of crossed sensitization and intoxication tests. Certain conclusions, however, can be drawn from an analysis of the results of this series.

An analysis of Table IV shows that it was possible to sensitize and to intoxicate guinea-pigs with the extract of a mixture of strains of several pneumococci, and with the ex-



TABLE IV.—THIS TABLE ILLUSTRATES THE ACTION OF EXTRACTS OF THE PNEUMOCOCCUS AND REPRESENTS A FEW RESULTS SELECTED FROM A LARGER SERIES.

No. of animal.	Wt. in gm.	Species to which sensitized.	Extract injected.				Result.		
			(a) Species.	(b) Wt. in gms. per 250 gms. of guinea-pig.	(c) Duration.	(d) Heated.	Reac- tion.	Outcome.	Autopsy.
25	360	Normal control.	Pneumococcus mixtures.	0.040	18 hrs. in ice box.	1 hr. 55° C.	0	Lived.	.....
121	460	Pneumococci; mixtures of strains.	" " "	0.040	" "	" "	+ + +	+ 7 min.	Typical lesions.
9	250	Normal control.	Pneumococcus (Gatches).	0.060	18 hrs. 37° C.	" "	0	Lived.	.....
154	460	Pneumococcus (Gatches).	" " "	0.040	" "	" "	+ + +	+ 5 min.	Typical.
124	450	Pneumococcus mixtures.	" " "	0.040	" "	" "	+	Lived.	.....

TABLE V.—THE ACTION OF EXTRACTS OF STR. PYOGENES.

No. of animal.	Wt. in gm.	Species to which sensitized.	Extract injected.				Result.		
			(a) Species.	(b) Wt. in gms. per 250 gms. of guinea-pig.	(c) Duration.	(d) Heated.	Reac- tion.	Outcome.	Autopsy.
79	270	Normal control.	Staph. pyogenes.	0.040	18 hrs. 37° C.	1 hr. 55° C.	0	Lived.	.....
112	300	" "	" "	0.060	" "	" "	0	"	.....
133	550	Str. pyogenes.	" "	0.040	" "	" "	0	"	.....
140	620	" "	" "	0.040	" "	" "	0	"	.....
141	670	" "	" "	0.060	" "	" "	+	+ over night.	Negative.
57	430	Str. viridans.	" "	0.060	" "	" "	0	Lived.	.....
93	270	Pneumococcus.	" "	0.060	" "	" "	0	"	.....

TABLE VI.—THE ACTION OF EXTRACTS OF STR. VIRIDANS.

No. of animal.	Wt. in gm.	Species to which sensitized.	Extract injected to intoxicate.				Result.		
			(a) Species.	(b) Wt. in gms. per 250 gms. of guinea-pig.	(c) Duration of extraction.	(d) How heated.	Reac- tion.	Outcome.	Autopsy.
113	300	Normal control.	Str. viridans.	0.060	18 hrs. 37° C.	1 hr. 55° C.	0	Lived.	.....
115	300	" "	" "	0.060	24 hrs. 37° C.	1 hr. 60° C.	0	"	.....
58	370	Str. viridans.	" "	0.060	18 hrs. 37° C.	1 hr. 55° C.	+ + +	+ 5 min.	Typical.
62	350	" "	" "	0.060	" "	" "	+ + +	" "	"
67	290	" "	" "	0.060	24 hrs. 37° C.	1 hr. 60° C.	+	.....	.....
95	300	Pneumococcus.	" "	0.060	18 hrs. 37° C.	1 hr. 55° C.	0	Lived.	.....
101	270	" "	" "	0.060	" "	" "	0	"	.....
142	660	Str. pyogenes.	" "	0.060	" "	" "	0	"	.....

TABLE VII.—THE ACTION OF EXTRACTS OF PNEUMOCOCCUS.

No. of animal.	Wt. in gm.	Species to which sensitized.	Extract injected to intoxicate.				Result.		
			(a) Species.	(b) Wt. in gms. per 250 gms. of guinea-pig.	(c) Duration of extraction.	(d) How heated.	Reac- tion.	Outcome.	Autopsy.
110	300	Normal control.	Pneumococcus (Gatches).	0.060	18 hrs. 37° C.	1 hr. 60° C.	0	Lived.	.....
78	250	" "	" "	0.060	" "	" "	0	"	.....
77	260	" "	" "	0.080	" "	" "	0	"	.....
53	330	Pneumococcus (Gatches).	" "	0.060	" "	" "	+ + +	+ 5 min.	Typical.
180	530	" "	" "	0.060	" "	" "	+ + +	Lived.	.....
94	340	Pneumococcus (Neufeld Pni).	" "	0.060	" "	" "	+	"	.....
130	600	Str. pyog.	" "	0.060	" "	" "	0	"	.....
59	500	Str. viridans.	" "	9.060	" "	" "	0	"	.....
114	320	Normal control.	Pneumococcus (Sam).	0.060	" "	" "	0	.....	.....
74	300	" "	" "	0.060	" "	" "	0	+ 2 hrs.	Negative.
22	710	Pneumococcus (Sam).	" "	0.045	" "	" "	+ + +	+ 3 min.	Typical.
105	720	" "	" "	0.045	" "	" "	+ + +	+ 6 min.	"
100	280	Pneumococcus (Neufeld Pni).	" "	0.060	" "	" "	0	Lived.	.....
64	410	Str. viridans.	" "	0.060	" "	" "	±*	"	.....
66	440	" "	" "	0.060	" "	" "	+ +	+ 5 min.	Typical.

\* Showed slight symptoms.



tract of a single strain of pneumococcus. It was found also that a guinea-pig, which had been sensitized to a mixture of several strains of pneumococci, could be intoxicated with the extract of a single strain, not included in that mixture.

It was not possible acutely to intoxicate guinea-pigs with extracts of *Str. pyogenes* prepared in this manner. Occasionally mild anaphylactic symptoms were elicited. Thus, No. 141 (Table V) showed restlessness after the injection, defecation and micturition, occasional hiccoughs, and pronounced respiratory distress. After 50 minutes these symptoms subsided; the animal showed great weakness, and died during the night. The controls, as well as an animal sensitized to *Str. viridans*, and to a pneumococcus, showed no symptoms. There was only a feeble intoxicating power demonstrable and this seemed to be specific.

Table VI demonstrates that sensitized animals can be acutely and fatally intoxicated by injections of extracts of *Str. viridans*. The results also indicate a considerable degree of specificity in the reaction, since animals which had been sensitized to the pneumococcus and to *Str. pyogenes*, did not show any anaphylactic symptoms. However, pigs Nos. 95 and 101 probably were not maximally sensitized since some of the other members of this series did not react on injection of pneumococcus extract. (See Nos. 100 and 94 in Table VII.)

This table (VII) shows, again, that guinea-pigs which have been sensitized to pneumococcus, can be intoxicated acutely by an intravenous injection of an extract of pneumococci. Such an extract did not cause any anaphylactic symptoms on injection into a pig sensitized to *Str. pyogenes*, but did fatally intoxicate one out of three pigs sensitized to *Str. viridans*, and caused very mild anaphylactic symptoms in one of the other two. The reaction is, therefore, not absolutely specific, but quantitatively a certain degree of specificity is shown by a comparison of this series with that summarized in Table VI, since pigs sensitized to *Str. viridans* uniformly reacted to injections of the corresponding viridans extract.

These results apparently showed a rather higher degree of specificity in the reaction in the differentiation of the pneumococcus and streptococcus, than was described by Rosenow<sup>8</sup> and by Davis.<sup>10</sup> But the method of preparing the material for the intoxicating injection used in these experiments was so different from their methods that the results are scarcely comparable.

The following experiments were carried out in order to demonstrate, if possible, whether any relationship exists between hypersensitiveness to extracts of the pneumococcus and immunity to living pneumococci in guinea-pigs. For this work the virulent strain of pneumococcus, already described, was employed. It was carried through a long series of guinea-pigs to maintain a high degree of virulence and, if possible, to increase its virulence for this species.

One series of guinea-pigs was sensitized, as described, by three subcutaneous injections of 0.020 gm. of dried, killed cultures, given on alternate days. After several weeks, some of these were reinjected intravenously with extracts of pneumococci, as illustrated in Table II, and were shown to be

highly sensitized. Other animals of the series (series B. Table VIII) were given subcutaneous injections of graduated doses of living virulent cultures to determine their degree of immunity. Rosenow<sup>8</sup> has shown that guinea-pigs suitably sensitized have a definite immunity of moderate degree to virulent pneumococci. This is to be expected, since it has long been known that a large dose of killed, virulent organisms produces a considerable degree of immunity in the rabbit.

Another series of pigs was immunized by repeated subcutaneous injections of small, increasing doses of living cultures. In some cases a single preliminary injection of killed organisms was given, followed later by injections of living organisms. One such dose of killed organisms alone did not cause the development of demonstrable hypersensitiveness. After a high degree of immunity had been secured, some animals of the series were given intravenous injections of an extract of pneumococci to determine whether hypersensitiveness also had developed. Other animals of this series (Series C, Table VIII) were given subcutaneous injections of living, virulent cultures to demonstrate that immunity had been produced.

The degree of immunity developed is illustrated by the following series:

TABLE VIII.

No. of animal.	Series A. Normal guinea-pigs.		Series B. "Sensitized" guinea-pigs.		Series C. "Immunized" guinea-pigs.	
	Dose in cc.	Result.	Dose in cc.	Result.	Dose in cc.	Result.
1	.....	.....	0.2	+ 9 days. Cult. +	0.2	Lived.
2	.....	.....	.....	.....	0.1	"
3	.....	.....	.....	.....	0.1	"
4	.....	.....	.....	.....	0.06	"
5	.....	.....	.....	.....	0.02	"
6	0.01	+ 11 days. Cult. +	0.02	Lived.	0.01	"
7	0.001	+ 5 days. Cult. +	0.002	+ 13 days. Cult. +	0.002	"
8	0.0001	Lived.	0.0002	+ 10 days. Cult. 0	.....	.....
9	0.00001	"	0.00002	Lived.	.....	.....
10	0.000001	+ 17 days. Cult. +	0.000002	"	.....	.....

The virulence of the strain was such that 0.001 cc. of a 24-hour serum-broth culture was the minimal dose which was certainly fatal for guinea-pigs. In several other series of guinea-pigs, injected to determine the virulence of this strain; doses of 0.001 cc., or less, were almost invariably fatal. Much smaller doses, even 0.000001 cc., were often fatal, but not regularly so. The animals which died showed a septicæmia at autopsy, but usually the number of organisms present in the blood was not large. The minimal fatal dose for mice and rabbits varied from 0.000001 cc. to 0.0000001 cc.

The survival of the sensitized pig, B No. 5, which received 0.02 cc., of a living culture is to be regarded as a definite indication of immunity, since no normal animal survived one-tenth as large a dose. But that such sensitization does not produce regularly any noteworthy immunity is shown by the death of two animals in the series which received smaller doses of the culture. The regularly "immunized" animals in series C were much more resistant, surviving 100 and 200 times the M. L. D. However, of the 32 animals in which immunization was attempted about three-fourths died in the process, and the



seven survivors in series C probably possessed an unusually high degree of natural resistance.

To test for hypersensitiveness, three of these immunized animals were given an intravenous injection of extract of pneumococci 4 weeks after the last injection of living culture.

TABLE IX.—REACTIONS OF IMMUNIZED AND SENSITIZED PIGS TO PNEUMOCOCCUS EXTRACTS.

No. of animal.	Wt. in gms.	Previous treatment.	Wt. in gms. of culture extract per 250 gms. of guinea-pig.	Duration of extraction.	How heated.	Result.		
						Reaction.	Outcome.	Autopsy.
110	300	None.	0.060	18 hrs. 37° C.	1 hr. 60° C.	0	Lived.	.....
111	350	"	0.060	" "	" "	0	"	.....
159	480	"Sensitized."	0.040	" "	1 hr. 55° C.	++	+ 5 min.	Typical.
160	460	"Sensitized."	0.040	" "	" "	++	" "	"
C., No. 3.	500	"Immunized."	0.060	" "	1 hr. 60° C.	++	" "	"
183		"						
C., No. 5.	330	"Immunized."	0.060	" "	" "	++	" "	"
53		"						
C., No. 2.	530	"Immunized."	0.060	" "	" "	++	Lived.	.....
180		"						

This table shows that Nos. 159 and 160 were highly sensitized. They had received the same preliminary injections of pneumococci to cause sensitization as had the animals of series B in Table VIII. It also shows that, with the higher grade of immunity produced by a series of injections of small doses of living, virulent pneumococci, a marked degree of hypersensitiveness to pneumococcus protein also developed. But that there is any direct causal relationship between these conditions, is not demonstrated by these experiments.

As is well known, in man a tuberculous infection often results in the development of marked hypersensitiveness to tuberculin. This is demonstrable in several ways, but is most simply and conveniently shown by direct application of the diluted tuberculin to the conjunctiva, as in the ophthalmic test of Calmette; or to the skin, as in the cutaneous test of von Pirquet, or on intracutaneous injection. Solutions which cause no symptoms in normal individuals, may cause a marked inflammatory local reaction in the hypersensitive tuberculous patient. The evidence is strongly in favor of the view that this local condition of hypersensitiveness is associated with, and due to, a general hypersensitiveness to tuberculo-protein. The evidence for this view has been well summarized by Hamman and Wolman.<sup>11</sup>

In this work, attempts were made to demonstrate in man an analogous condition of hypersensitiveness to pneumococcus protein by instillations into the conjunctiva, and by intracutaneous injections. As these preliminary tests were unsuccessful, no attempt was made to demonstrate such a possible hypersensitiveness by transferring it passively to guinea-pigs, by injections of the patient's blood or serum. There seemed no prospect of success, in view of the fact that a similar passive transfer to guinea-pigs of hypersensitiveness to tuberculo-protein in man, is very rarely demonstrable,<sup>12</sup> although marked local reactions of the skin and conjunctiva in man are frequently obtained.

A protein precipitate, the activity of which had been demonstrated by its power to intoxicate sensitized guinea-pigs (see Table III), was dissolved in physiological salt solution, to form a 1 per cent solution; and heated 1 hour at 60° C. If suitable, it dissolved readily and formed a slightly opalescent, colorless solution. If dark in color, or turbid, it was centrifugalized till clear and reprecipitated. Filtration through a Berkefeld filter was avoided because it was thought that the activity of the material might be lessened in the process. A small quantity of the solution was instilled into the eyes of several normal and sensitized guinea-pigs, and also into the eyes of several normal and immunized rabbits. Subcutaneous and intracutaneous injections were also made. As the solution was found to be quite harmless to these animals, it was employed on patients. After being dissolved, the material was kept on ice over night, before use on patients; but it was never used, if more than 24 hours old.

An eye test was made by instilling a drop of a 1 per cent solution into the conjunctival sac of one eye. The usual precautions taken in carrying out a Calmette reaction were observed. The eyes were examined and carefully compared several times during the following 36 hours.

In all, there were tested 15 patients with pneumonia and, as controls, 20 patients, suffering from a variety of other conditions. In 2 of the former 15, tested at or near the crisis, there developed reactions of moderate severity. In from 4 to 6 hours there appeared a moderate fibrino-purulent discharge, with definite congestion of the palpebral conjunctiva and caruncle, and some dilatation of the bulbar vessels. There was some lacrymation, and slight discomfort. The difference in appearance of the two eyes persisted for 24 hours.

In 4 other patients with pneumonia there developed a slight, but definite, congestion of the caruncle and palpebral conjunctiva of the eye tested, with a small amount of exudate. In 1 control, a colored man with tuberculous peritonitis, a similar reaction was obtained. These mild reactions all subsided within 24 hours. The other 9 patients with pneumonia and the 19 controls gave no reactions.

A cutaneous reaction was also tried in 7 cases of pneumonia and in a number of control patients. In some cases the skin was scarified, as for a von Pirquet reaction, and a drop of a 1 per cent solution of the protein applied and allowed to dry.

In all of these 7 cases intracutaneous injections were made of 0.05 cc. of a 1/10 to 1/100 per cent solution of protein. The injection of this amount of a 1 per cent, or a 1/4 per cent solution in man caused painful inflammatory reactions that subsided after 24 hours, although they caused no reaction in guinea-pigs or rabbits. The injection of the more dilute solutions caused milder reactions that were but little, if any, more outspoken in the patients with pneumonia than in the control patients. A discrete papule usually developed, 0.5 to 2.0 cm. in diameter, surrounded by an ill-defined area of hyperæmia. It was usually but slightly elevated. In some cases there was a more diffuse swelling of the surrounding tissues. Although actual measurements of the papules averaged a little larger in pneumonia patients than in the control cases, the difference



was slight and not constant. There was no difference in the reaction at different stages in the disease, either early in the acute stage, at the crisis, or late in convalescence.

#### SUMMARY.

By means of a slight modification of Besredka's method, a "protein" extract was obtained from pneumococci which would sensitize normal guinea-pigs, and which would specifically intoxicate suitably sensitized guinea-pigs. But it was not found possible to prepare extracts in this way which uniformly caused acute fatal reactions in sensitized animals.

During the process of extraction, as pointed out by Rosenow, a certain degree of autolysis apparently occurs, which causes the extract to acquire a considerable degree of toxicity, if the extraction is too prolonged. Heating one hour at 60° C. greatly reduces the toxicity, but does not always entirely destroy it. Normal animals, which die from the intravenous injection of such toxic extracts, show practically the same symptoms, and the same findings at autopsy, as do animals that die in typical anaphylactic shock.

There is quantitatively a certain degree of specificity in the reactions of suitably sensitized animals to extracts of pneumococcus and *Str. viridans*; probably also in reactions to these extracts and to extracts of *Str. pyogenes*; but this specificity is not absolute.

Guinea-pigs sensitized with extracts of pneumococci showed inconstantly a very slight grade of immunity to infection with living, virulent cultures. Animals highly immunized by repeated subcutaneous injections of living, virulent cultures, showed also a marked degree of hypersensitiveness to pneumococcus extracts.

It was not possible to demonstrate a condition of hypersensitiveness to pneumococcus "protein," in patients with pneumonia, by the local application of a solution of the protein to the conjunctiva or by intracutaneous injections.

In conclusion I wish to thank Dr. Lewellys F. Barker for permission to carry out and report this work, and for his constant encouragement and advice.

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#### IN MEMORIAM.

JAMES G. MUMFORD.

The Johns Hopkins Hospital Medical Society desires to place upon record its appreciation of the life and work of Dr. James G. Mumford, who died at Clifton Springs, New York, October 18, 1914. Upon different occasions, Dr. Mumford has honored this society by presenting papers on various topics and always of unusual interest and merit. This is true also of The Johns Hopkins Hospital Historical Society. Dr. Mumford was a many-sided man. As a surgeon, he early achieved distinction in his chosen profession, where, among other characteristics, his sound judgment and keen perception were especially noteworthy. As an author and historian, his clarity of diction and elegance of expression, together with accuracy of statement and sterling honesty of purpose, combined to place his writings far above the ordinary. As a friend and companion, it would be difficult to find a more charming and winsome personality, always affable, courteous and tolerant of the opinions of others, yet firmly tenacious of principle and ever ready to defend the right as he saw it. His indomitable courage and unfailing cheerfulness, in the face of ill health and enforced retirement from the active practice of surgery, were an inspiration to those who knew him. Therefore, be it

*Resolved*, That in the untimely death of Dr. James Gregory Mumford, the medical profession has lost one of its ablest and most productive members, and that we, as a society, have lost an honored and trusted friend. And be it further

*Resolved*, That a copy of these resolutions be spread upon the minutes of this society, be printed in THE JOHNS HOPKINS HOSPITAL BULLETIN and be sent to Mrs. Mumford.

HENRY B. JACOBS,

J. M. T. FINNEY,

Committee.



# THE RECOGNITION OF ATYPICAL FORMS OF INTESTINAL AMOEBIASIS.\*

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AND

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## OUTLINE.

### I. Introduction:

1. Frequency of diarrhoeas of obscure origin.
2. Lack of variation in the classical picture of amoebic dysentery.

### II. Clinical description of these obscure cases:

1. General type of case.
2. Contrasts between these and cases of amoebic dysentery;
  - A. Continuous course of symptoms,
  - B. Mildness of symptoms,
  - C. Character of stool,
  - D. Lack of response to emetine,
  - E. Absence of characteristic amœbæ in the stools.
3. Occasional points of similarity.

### III. Investigation of the ætiology of three cases of diarrhoea:

1. Essential features of the clinical examination of these patients.
2. Investigation of the amœbæ occurring in these cases;
  - A. Morphology,
  - B. Pathogenesis,
    - a. Clinical effect in animals,
    - b. Morphology of the amœbæ in animals,
    - c. Pathologic lesions in animals.

### IV. Relationship of various strains and species of amœbæ:

1. *E. histolytica*,
2. *E. coli*,
3. *E. limax*,
4. Unidentified strains.

*Introduction.*—In the past few years there have come to light some rather surprising instances of the confusion between parasitic and non-parasitic diseases. Ordinarily, the clinical symptoms of these two groups of conditions are sufficiently distinct to differentiate them sharply, but cases have been encountered in which the distinction, based upon clinical grounds alone, was erroneous, as in infantile paralysis and in the metabolic types of peripheral multiple neuritis such as the predominant form of beri-beri. In some conditions, notably in dermatology, difficulty arises in the distinction between parasitic and metabolic conditions because of the comparatively mild nature of the disease and the absence of any outspoken distinctive symptoms. A similar confusion suggests itself in certain diarrhoeal diseases in man, in view of the comparative mildness of the symptoms and the manifold causes that must be considered.

In the present paper we shall consider the ætiology of some obscure cases of dysentery and diarrhoea occurring here in Baltimore during the past winter. Our attention has been directed especially toward three cases which represent fairly distinct types of conditions. One of these patients (A) was

a negro from the West Indies. He gave a history of a luetic infection; the blood serum gave a positive complement fixation with luetic antigen and proctoscopic examination showed the findings characteristic of a syphilitic proctitis. A continuous diarrhoea had been present for some years. These findings led to the conclusion that the diarrhoea was due to the anatomic changes occurring in the mucosa of the sigmoid and rectum, resulting from the syphilitic infection. The second patient (B) was a boy of 14 years, who presented the anatomic conditions of Hirschsprung's disease accompanied by a diarrhoea of long standing. This latter symptom was interpreted as the result of the extensive dilatation and the loss of function of the bowel incident to the development of a giant colon. The third case (C) was one of distinctly atypical amoebic infection.\*

In the consideration of the ætiology of an obscure diarrhoea, perhaps the first distinction to make is the differentiation between the parasitic group and those of non-parasitic origin, such as occur in the condition of achylia gastrica, or those conditions like the case of Hirschsprung's disease, just mentioned, where the anatomic condition would presumably account for the diarrhoea. We have been interested especially in those patients in whom the possibility of amoebic infection is to be considered.

The symptoms of amoebic dysentery in man are remarkably constant, there being comparatively little variation in the classical picture. The disease is indeed a far from simple one, inasmuch as it is often accompanied by many complications. Moreover, the differences between the acute and chronic types are often very sharp. A third group of cases has been described by Strong<sup>1</sup> in which the symptoms are comparatively mild. Slight prodromal disturbances may exist for several months, the condition terminating eventually either in recovery or in a frank typical dysentery. It will be seen that this condition is essentially different from that of a persistent watery diarrhoea.

Apparently all cases of amoebic infection, when well established, conform to the usual picture of either the acute or chronic stage. Even in heavily infected endemic zones, one finds little evidence of atypical or unusual cases. Thus, so far, no success has been attained in the attempt to attribute an amoebic ætiology to hill diarrhoea, such as occurs in India or in the summer capital of the Philippines in the Benguet Mountains and other hill stations of Asia. Indeed, it would seem that, like other longstanding protozoan infections, such as

\* Presented at the eleventh annual meeting of the American Society of Tropical Medicine, held in Boston, May 29, 30, 1914.

\* This patient was seen through the kindness of Dr. Earle and Dr. Sexton of the visiting and resident staff of the Hebrew Hospital.



malaria and trypanosomiasis, the symptoms of amœbic infection remain remarkably constant. But in looking for unusual chronic types of infection, it is conceivable that these might occur, not primarily in the tropics, where the optimal conditions prevail for the development and propagation of the disease, but rather in the north, where the disease must maintain itself under unusual and adverse conditions. Accordingly, we have examined some of the atypical cases of diarrhœa in various ways in order to detect, if possible, unusual examples of amœbic infection.

*Clinical Description of Obscure Diarrhœas.*—In those cases of diarrhœa which came under observation, there were certain general features which were characteristic of the group, though, of course, the symptoms of the individual patients varied among themselves. For the most part, the general health of the patient was comparatively good and the principal symptom was the annoyance of frequent stools. The disease, when once established, ran a continuous course over a period of several years, free from any intermission or remission of symptoms. The stools were usually frequent, containing much water, but little or no mucus and blood. Microscopical examination of these cases sometimes showed amœbæ, but the characteristic *Entamœba histolytica* was absent. Moreover, the amœbæ in these cases did not disappear after injections of emetine; neither did the symptoms yield to this therapy. Such cases present a marked contrast to the typical chronic cases of amœbic dysentery, in which periods of apparent health alternate with acute relapses, the relapse being characterized by the appearance of bloody mucous stools rich in amœbæ, but the parasites and symptoms disappearing temporarily, either spontaneously or upon the injection of emetine. In view of the relative constancy of the essential features of chronic amœbic dysentery, it would seem that there is little ground for any correlation of these cases of diarrhœa with amœbic infection. In the details of the histories of these patients, there are but few points of similarity in common with amœbic dysentery. Perhaps it is significant, though, that the symptoms were of several years' duration in two of these patients and in the early days of the disease at least a definite dysentery had existed; while one of these patients was under observation, periods frequently occurred in which a considerable quantity of blood appeared in the stools, but in the intervals between these hemorrhages, the watery diarrhœa continued.

*Considerations in Regard to the Diagnosis of Amœbic Dysentery.*—In considering the interpretation to be placed upon the occasional appearance of amœbæ in these cases, it is necessary to discuss briefly the basis on which it is permissible to diagnose amœbic dysentery and the significance of the occurrence of amœbæ in the intestinal tract. For the present we feel that it is necessary to accept the view that *there are but two parasitic amœbæ of man, one of which, E. histolytica, is pathogenic, and the other, E. coli, though parasitic, is non-pathogenic.* In order to make a diagnosis of amœbic dysentery the clinical symptoms must be present, and it is also necessary to demonstrate the presence of *E. histolytica*, though, for practical purposes, one is perfectly safe in diagnosing dysentery when a

patient is passing bloody mucous stools, containing numerous active amœbæ.\* Hypothetically one would have to guard against the occurrence of a bloody, mucous dysentery of neither bacillary nor amœbic origin in a patient already harboring *E. coli*; but, in such a condition, the conservative course, from a clinical standpoint, would be to use emetine therapy. Furthermore, mixed infections with the two species of entamœbæ are so common that the presence of *E. coli* in a case of dysentery would in no sense militate against the simultaneous occurrence of *E. histolytica*, even though it could not be demonstrated microscopically at all times. However, as in many bacterial conditions, comparatively little reliance can be placed upon the establishment of the presence of pathogenic entamœbæ in the intestine without considering also the clinical condition of the patient. Unlike what occurs in trypanosomiasis and malaria, such perfectly typical carriers<sup>2</sup> develop that the occurrence of *E. histolytica* in the stools does not necessarily prove the presence of any diseased condition. Indeed, in addition to the carriers resulting from a typical attack of dysentery, individuals are sometimes found with virulent four-nucleated cysts of *E. histolytica* in the stools, who, as far as they know, have never had any symptoms of dysentery.<sup>3</sup> The diagnosis, therefore, is extremely easy in a typical case during an acute attack. However, when only indefinite symptoms occur accompanied by the presence of amœbæ in the stools, then it becomes much more important to identify the species absolutely. In cases where only a mild diarrhœa exists and where only an occasional amœba is found in the stools, which cannot be identified with *E. histolytica*, then the diagnosis of amœbic dysentery would not be justified, especially where other causes of diarrhœa are present. We have studied such cases as this during the winter of 1913-14, to determine, if possible, the ætiologic factor involved. This has been approached by examining these patients for various conditions that might be responsible for the diarrhœa, and by studying the amœbæ occurring in these cases, especially with regard to their identity as determined by their morphology and their pathogenicity for animals.

*Identification of the Parasitic Amœbæ.*—The identification of the two parasitic species of amœbæ which may occur in the human intestine cannot be determined by animal inoculation, even though the one species is pathogenic and the other harmless, on account of the frequency of mixed infection with both species, and the uncertainty of animal inoculations. Thus, the pathogenic species may fail to produce dysentery upon inoculation, and it is always possible that a stool in which the non-pathogenic species predominates may produce dysentery on account of the presence of a few pathogenic forms that have

\* We have used the term amœbæ in a very general sense, applying it to the parasitic, as well as free-living amœbæ; for certainly, in a vernacular sense, the entamœbæ belong to the larger group of amœbæ. In cases where the distinction between the free-living and parasitic forms is not perfectly clear from the context, the term entamœbæ has been used. It is certainly necessary to have a term which may be applied to either the free-living or the parasitic group, especially in discussing a form of which the identity has not been established.



been overlooked microscopically. Accordingly the distinction must be made by the differences in the morphology of the two species. In typical dysentery from *E. histolytica* and in normal individuals carrying *E. coli* it is comparatively easy to recognize the morphological differences which have been described in the two types of trophozoites. But in chronic cases, which are healing, in which there is comparatively little blood and mucus for the amœbæ to feed upon, and in which the bowel is approaching its normal condition, Walker<sup>3</sup> has pointed out that the trophozoites of *E. histolytica* approach those of *E. coli* in their morphology and the distinction between them becomes much more difficult. Indeed, it may be necessary to see the propagative stage in order to determine whether the cysts contain the classical number of four nuclei or eight, before we can identify the species. These observations are of especial importance in our own cases, since we were dealing with such chronic types. Accordingly, in addition to the study of the trophozoites, we have taken precautions to secure stained specimens of the propagative stage as well. In testing the pathogenicity of these amœbæ, upon animal inoculation, it seemed advisable to take special precautions, in view of the mildness of the symptoms and the scarcity of the organisms in these cases. Accordingly, we have depended largely upon the technique of exposing the cæcum under general anæsthesia and inoculating directly into the lumen against the mucosa of the bowel.

*Ætiology of These Diarrhœas of Obscure Origin.*—For a thorough analysis of the symptoms presented by these patients, the following details of their records are helpful:

CASE A.—This patient, aged 40, a negro from the Cape Verde Islands, had had two diseases in the past that are important in connection with his present condition. About 15 or 20 years ago he contracted syphilis and apparently received but little treatment. About 10 or 12 years ago, while in Egypt, he contracted a typical bloody mucous dysentery. The exact details of these early symptoms are forgotten, but apparently intermissions in the symptoms occurred during the early years of the disease, such as are typical of the amœbic form of dysentery. In the past few years, however, there had been no intermission in the symptoms with periods of apparent health, such as one expects to find in amœbic infection. The patient gave a history of passing as many as twenty stools per day. These were very watery, and contained practically no mucus, and no blood except for occasional bleeding from some external and internal hæmorrhoids.

*Physical Examination.*—The patient was somewhat undernourished. The cardiovascular system was normal except for fairly well-marked atherosclerosis. The abdomen was slightly tense and also somewhat tender on deep palpation, especially near the median line below the umbilicus. The thickened sigmoid was readily palpable. Proctoscopic examination showed a very marked proctitis with ulcerations of the mucous membrane, which bled readily and were covered with a purulent discharge. In some areas the induration of old scars could be seen. The condition suggested very definitely a luetic proctitis. The blood serum gave a positive Wassermann reaction. Examination of the stools for parasites, after purging, showed numerous flagellata, and an occasional small, sluggish amœba. Cultures for *B. dysenteriae* were negative.

From these data it is seen that the picture was a somewhat complicated one, but the weight of evidence seemed to indicate definitely that the symptoms then present ought to be ascribed to a

luetic proctitis. The patient was given 0.6 gm. of salvarsan intravenously. Within three days the number of stools decreased from about 10 to one or two per day, the flagellates diminished markedly in number, and the amœbæ disappeared completely. Within 10 days after the injection of salvarsan, however, the number of stools gradually increased to five or six per day, the flagellates returned, and occasionally the trophozoite of an amœba was found. Injections of emetine in doses of  $\frac{1}{2}$  of a grain daily, for eight days, failed to control the diarrhœa. The vegetative amœbæ disappeared from the stool, but cyst-like bodies were constantly present.

CASE B.—The second case was that of a school boy, aged 14, who came to the hospital, in December, 1913, complaining of pain in the stomach and diarrhœa. About 9½ years ago the patient contracted a diarrhœa of gradual onset lasting only a few weeks, and assumed to be only "summer complaint." This diarrhœa returned in the following summer, three to five stools being passed in the 24 hours, with an occasional discharge of blood during the first few weeks after the return of symptoms. It has persisted almost continuously since that time, principally as a watery diarrhœa. During the past year the patient has had dull pains in the stomach, especially after meals, and the "stomach" began to grow to a relatively enormous size. Recently the patient has been losing weight and becomes tired very easily.

*Physical Examination.*—The patient was a sparely nourished, frail-looking boy, distinctly sallow and small for his age. The temperature ranged from 100° to 101° F., with a leucocyte count of 6000. The lungs were normal except in the left interscapular region, where there was broncho-vesicular breathing. The Calmette reaction with tuberculin was negative. The abdomen was markedly and rather uniformly distended, with the costal margins flared out, the iliac grooves practically obliterated and the lumbar curves bulging slightly. The sigmoid was readily palpable, but the enlargement appeared to be due chiefly to the dilatation of the colon. The X-ray examination showed a redundant sigmoid with spastic dilatation of the remaining colon, suggesting a true obstruction, such as would be caused by a fibrous band just above the sigmoid. These findings led to the diagnosis of Hirschsprung's disease with the possibility that a chronic inflammatory process, such as tuberculosis, was superimposed on this condition.

An examination of the stools showed the presence of red blood cells, numerous flagellata, and a few non-motile trophozoites of amœbæ. In the third week after admission to the hospital this boy complained of acute cramps in the abdomen. The stools at this time were copious and contained moderately large amounts of fresh blood. On microscopic examination, moderate numbers of sluggishly motile amœbæ were found.

Inasmuch as these chronic cases yielded very poorly indeed to either emetine or ipecac therapy, we used a decoction of chaparro amargosa as recommended by Nixon.<sup>4</sup> In the course of a week, however, it was found necessary to discontinue it on account of the nausea that developed. Even in this length of time, however, the flagellata and amœbæ diminished definitely in numbers and the amount of hæmorrhage from the bowel was markedly reduced. For further treatment, surgical interference was decided upon and the patient was transferred to the surgical service of this hospital. An appendectomy and a cæcostomy were performed. In addition to the enlargement of the cæcum and colon, a condition of adiposis epiploicæ was found, the pelvis being practically filled with fat. Irrigations with quinine solutions were carried out, beginning with 1:5000 and increasing to 1:750 within six weeks; and this strength was continued for a period of three weeks. During this time the symptoms improved considerably. The stools, though still unformed, were distinctly less watery and contained only traces of blood. On microscopical examination it was found that the flagellata had disappeared entirely and only a few cysts of amœbæ were present.



CASE C.—The third case was somewhat different from either of these. The patient did not give a definite history of amœbic dysentery at any time in the past, but attacks of diarrhœa had occurred frequently. This symptom had been constantly present for the past 18 months and had proven very refractory to therapy. When first seen by Dr. Earle and Dr. Sexton, vegetative amœbæ were present in the stool, but their morphology was not sufficiently characteristic to permit of identification. A few days later, on proctoscopic examination, several discrete ulcers with rolled edges were seen in the mucosa of the rectum. Scrapings from these contained cyst-like bodies with two and three nuclei, but neither trophozoites nor four-nucleated cysts were found. This patient was treated with emetine in one-grain doses for about one week, and with ipecac in 80-grain quantities on two successive nights, but with comparatively little benefit.

*Investigation of the Amœbæ in These Cases.*—The amœbæ found in these cases were studied in several ways to determine whether they bore any ætiologic relationship to the symptoms occurring in these patients. First of all, the morphology was studied, both in the vegetative and propagative phases. In one case (A) a series of cultures was made on a special agar-agar to test for the presence of the limax group. The tests for pathogenicity were carried out by the inoculation of kittens. Inasmuch as case A was, in many respects, the most important of these three, it will be discussed first.

*Morphological Characteristics.*—The examination of fresh preparations of the stool of this patient showed numerous flagellata and an occasional amœba. It was evident that the flagellates might, in part, be responsible for the continuance of this diarrhœa once it had been inaugurated, but it did not seem that the amœbæ present could be playing any very active part. In the first place, they were extremely scarce, the trophozoites appearing only after the administration of salts, a condition often occurring in the infection of normal individuals with the harmless *E. coli*. In the unstained preparations the amœbæ were rather small in size and very sluggishly motile, the cytoplasm was somewhat hyaline in appearance and, correlated with the sluggish motility; the ectosarc and endosarc were not differentiated. The amœbæ were also free from red blood cells inasmuch as there was no bleeding from the mucosa. The nucleus could be seen rather easily and tended often to occupy a somewhat concentric position; on staining\* its characteristics were not typically those of either *E. coli* or *E. histolytica*. The nucleus was distinctly richer in chromatin than in either of these species, and it was arranged in rather large irregular masses.

\* For the staining technique see Baetjer and Sellards, Bull. Johns Hopkins Hosp., 1914, XXV, 165.

In the illustrations in the following plates, it will be noticed that frequently the nucleus is relatively large compared with the size of the cell. This characteristic increases the difficulty which sometimes arises in distinguishing, in stained preparations, between the cells of the host and the amœbæ. In order to control this, we have studied various materials stained with hæmatoxylin in the same way as the amœbæ. Pus cells from several sources were examined in view of their possible confusion with cysts. In addition to some smears of normal mucosa, preparations were made at varying intervals from mucosa which was allowed to digest in the thermostat, in order to secure examples of the slightly amœboid metazoan cells.

A search for the propagative stage revealed many cyst-like bodies containing one, two, and three nuclei, but after examining five preparations, we found only one of these bodies with four nuclei. In view of these rather gross differences it did not seem necessary to make an elaborate comparison of the finer details of structures in these various strains at this time. The general characteristics of these strains suggested some of the degenerative types which have occasionally been described as distinct species, such as the *E. minuta* of Elmassian (1909), which is probably a strain of *E. histolytica*; or the *E. nipponica* of Koidzumi (1909). This amœba was classified originally by Walker<sup>3</sup> as an aberrant form of *E. coli*, and by Hartmann<sup>5</sup> as a degenerated form resulting from the deterioration of either *E. coli* or *E. histolytica*. It was evident, from a microscopic examination of their morphology, that these amœbæ could not be placed definitely in either the histolytica or coli group. The general characteristics of the amœbæ seen in this case, therefore, in connection with the clinical findings, does not justify a diagnosis of amœbic dysentery. An ætiologic rôle could be ascribed to these amœbæ only if it could be clearly proven that they possessed definite pathogenic properties. On the other hand, it is necessary to exclude the possibility that these forms may be a saprophytic species.

*Attempts at Cultivation.*—On account of the comparative richness of the nucleus of some of the forms in chromatin and the frequency of uninucleated cysts, it seemed advisable to rule out the possible presence of some of the limax group. Some evidence has accumulated which suggests that, under favorable conditions, members of the limax type may not only pass through the intestine mechanically, when ingested with food, but that they may even colonize temporarily. Ordinarily, the occurrence of even a few trophozoites in the fæces is acceptable evidence that the form in question is not one of the free-living species. In order to exclude it rigidly, however, cultures were made, at intervals of two or three days, over a period of one month. These cultures were made as a routine on an agar medium based on Musgrave and Clegg's<sup>6</sup> work. Since the amount of alkali used in this medium may exert a pronounced influence, we used, not only 2 per cent of normal sodium hydroxide, but varying quantities, from none to 2 per cent. Duplicate cultures were sometimes made by inoculating highly diluted broth, dextrose solutions, and even distilled water, with varying amounts of fæces, since under special conditions these fluid media occasionally give very good results. These solid and fluid media were prepared according to the technique used in previous work with cultures of free-living amœbæ.<sup>7</sup> The results were constantly negative at all times on the various media. Suitable controls were carried out to demonstrate the efficiency of the agar media for the cultivation of the limax group. These consisted in the inoculation of agar tubes with a culture of limax, isolated originally from a case of amœbic dysentery, in the recovery of this culture from the stools after injection into animals, and also by demonstration, by cultural methods, of two species of the limax group occurring spontaneously in a normal kitten. These two species had not colonized, but evidently had been ingested with food



and were passing through the bowel mechanically, for the stool was entirely negative for cysts and trophozoites on microscopic examination, and after two days the cultures became negative for amœbæ.

The details of the control experiments of the animals injected were as follows: Two half-grown kittens were purged and examined for amœbæ, but no cysts nor trophozoites were found. Cultures on amœbæ agar remained free from amœbæ. On the next day each animal was injected, directly into the cæcum, with a suspension in 0.2 per cent salt solution of the growth of three agar slants of a culture of a limax amœba, containing an abundance of trophozoites and cysts, a culture being used which was known to be capable of passing mechanically through the alimentary tract of man.<sup>8</sup> Specimens of stools, obtained with a rectal tube, were examined each day for a week, both microscopically and culturally. No trophozoites nor cysts were seen at any time. The amœbæ were readily recovered on agar plates from both animals during the first four days after the injection. The plates on the fifth and sixth days remained free from amœbæ. This period of four days is certainly not longer than would be required for the intestinal tract to free itself mechanically from the large quantity of the culture which was injected; and the absence of amœbæ on microscopical examination is good evidence that no colonization took place. This behavior of these amœbæ in kittens corresponds exactly to their behavior in man. One of these kittens was sacrificed on the sixth day. No inflammation of the bowel was present, the mucosa being entirely normal. Cultures and microscopic preparations from the mucosa and the intestinal contents of the colon were entirely negative for amœbæ. The second cat was kept under observation for two months, but developed no clinical symptoms whatever. The cultivation of the limax amœbæ from the stools, especially in the case in which two species occurred spontaneously, is sufficient evidence that a satisfactory technique was used. In view of the repeatedly negative results obtained over a long period in the attempt at cultivation, it is evident that the amœbæ seen on microscopical examination were not members of the limax group.

*Determinations of Pathogenesis.*—One of the cardinal points in the examination of the strains of amœbæ occurring in these patients is the determination of their pathogenesis. In view of the high percentage of failures upon inoculation of virulent *E. histolytica* into kittens, it seemed very unlikely that the few atypical forms occurring in this patient would produce any effect. Nevertheless, since *E. coli* can colonize in kittens, it was evidently desirable to determine the fate of these amœbæ after inoculation. Accordingly, a kitten about one-third grown was selected for inoculation; microscopic examination of stool specimens obtained with the high rectal tube and by purgation with magnesium sulphate showed no form of protozoa. The injections were then made in three places; namely, into the cæcum, into the ileum about one foot above the ileocæcal valve, and into the stomach, a total of 6 cc. being used in each location. The specimen used for inoculation was rich in flagellates, but contained not more than one or two vegetative amœbæ in a

coverslip preparation, and no four-nuclear cysts, though cyst-like bodies with one, two, and three nuclei were abundant. Frequent examinations of the stools were made during the next few weeks, but no amœbæ nor flagellates were found and no clinical symptoms appeared. In the fifth week, however, one month after inoculation, frequent unformed stools were passed and these contained a few motile amœbæ. Examination, after salts, showed moderately large numbers of amœbæ, but no flagellates in either the active or encysted stage. Moreover, the amœbæ, though moderately abundant, were never excessively numerous, as in typical dysentery in man and animals. Cultures for the limax group remained entirely negative. The diarrhœa continued, the stools gradually becoming somewhat more watery and rather more frequent. The stools were free from blood and mucus, however, and tests for blood with guaiac were negative. Bacteræmia, which was found to accompany infections with typical *histolytica* almost constantly in young kittens,<sup>9</sup> did not develop in this animal; on the contrary, its general health was unimpaired and its growth continued rapidly. The amœbæ occurring in this animal were slightly larger and more active than those seen in the patient, there being some differentiation between ectosarc and endosarc. On staining, the nucleus was poorer in chromatin, as compared with some of the forms seen in the patient, but it was still distinctly richer than is the case with *E. histolytica* and *E. coli*. The impression obtained from observation of the trophozoites was that their resemblance to the *histolytica* type had increased after a single passage in animals. This change was seen not only in the nucleus, but also in the larger size of the organisms, their increased mobility, and the slight differentiation between ectosarc and endosarc. Changes of even greater significance occurred in the propagative stage. Cysts with four nuclei were not very uncommon and occasionally as many as five or six nuclei were found. In the cysts occurring in the patient, it will be remembered that four nuclei was the absolute maximum, the predominant numbers being two and three.

After the symptoms had persisted for two months, the diarrhœa began to diminish slightly and the amœbæ became somewhat less numerous. No blood appeared microscopically, but at times after extraction of the acidified stool with ether, a positive reaction was obtained with guaiac. At this stage the animal was sacrificed. The large bowel showed a few small hyperæmic areas, but no definite lesions were present. Moderate numbers of amœbæ were found and these were used for the intracæcal injection of two young kittens. The incubation period in one was five and in the other 10 days, though it must be noted that the material used for inoculation was much richer in amœbæ than in the first transfer from the patient. In the second passage mucus was occasionally present. No blood was seen except on microscopic examination, but the guaiac test for blood in the ether extract of the stool was positive. The kitten showing an incubation period of five days died on the following night, though presumably not from the amœbic infection, but from some unknown cause. At autopsy the large bowel showed a moderate degree of hyperæmia in some areas, but no other changes. Amœbæ were fairly abundant in the contents of the



bowel. They were not very well preserved, but apparently approached the histolytica type. The second animal died at the end of the third week after inoculation. The small bowel was intensely injected in the lower half of the ileum, the hyperæmia ending sharply at the ileocæcal valve. The contents of the large bowel were sero-purulent and contained many amœbæ. There was, however, no definite ulceration of the large bowel. The amœbæ were smaller in size than the usual parasitic forms, but they definitely resembled the histolytica type more closely than the forms originally seen in the patient. Inoculations were made from this animal into two kittens, one being inoculated by rectal tube, and the other intracæcally.

The animal inoculated by rectal tube died four days later. At autopsy there were no signs of amœbic infection. The animal inoculated intracæcally died on the third day of peritonitis. The stools, however, contained active amœbæ and the mucosa over the lower half of the rectum showed well-marked diffuse injection. Stained preparations of the amœbæ were not obtained during life and at autopsy they were not sufficiently well preserved to permit careful study.

In the second case (B) the amœbæ were somewhat intermediate between the coli and histolytica types, but here also the comparative richness of the nucleus in chromatin would not permit of a definite diagnosis of *E. histolytica*. Inoculations were made into a kitten during one of the periods when the patient was passing a considerable amount of blood. After an incubation period of three days a sharp attack of dysentery occurred, characterized by copious stools containing numerous flecks of blood and mucus with numerous amœbæ. This attack ended promptly in recovery before any entirely satisfactory specimens were obtained for morphological study.

The third case was rather different from these two, in that we were not able to find any trophozoites in the period during which this case was under observation. Material from the scrapings of the ulcers was comparatively rich in cyst-like bodies containing from one to three nuclei, but no four-nucleated forms were found. A kitten was inoculated with this material into the cæcum and into the stomach. After an incubation period of one month, a watery diarrhœa developed, corresponding to that seen in the patient. The amœbæ were fairly abundant, especially after purging. They did not differ essentially in morphology from those seen in the first transfer from the first patient (A). Since no trophozoites from this patient (C) were available for comparison with those in the subpassages, this strain was not carried any further. The symptoms in this kitten persisted continuously for about one and a half months and then became very much milder. After two months the animal was sacrificed; no evidences of amœbic infection could be found, either in the anatomical or microscopic examination of the bowel.

The results of these animal inoculations are significant, both in the interpretation of the ætiologic relationship of the amœbæ to the symptoms of these patients, and also in the determination of the relationship of these strains of amœbæ to the two parasitic forms in man. It is evident that the amœbæ occurring in these cases are pathogenic for kittens. The dupli-

cation of the characteristic symptoms of the patient in kittens and the exclusion of other adequate causes of diarrhœa justify the conclusion that the amœbæ were the ætiologic factor in producing the symptoms seen in these patients. This conclusion is especially clear, since the flagellata, present in great abundance in two of these patients, did not even colonize when inoculated into kittens.

*Comparison of Various Species of Amœbæ.*—The identity of the amœbæ occurring in these atypical cases, however, is not entirely clear. Accordingly, we have compared them in their morphology and pathogenesis with the better-known types; namely, *E. histolytica*, *E. coli*, and one member of the *limax* group. The strain of histolytica was obtained during an acute relapse in a typical chronic case from North Carolina. Examples of *E. coli*, for morphological study, were obtained from a cardiac case in a boy of 19, who had never been south of Maryland and had never had any symptoms of dysentery. The strain of limax was one which was cultivated from a perfectly typical case of amœbic dysentery during an acute stage in a patient living in Manila. The inoculation of animals with these strains was carried out by injection into the cæcum.<sup>10 11</sup> Although it has been shown definitely that cultures of the limax group can neither produce symptoms nor colonize in man, yet for completeness' sake two kittens were inoculated with overwhelming quantities of a culture of free-living amœbæ. The failure to produce any symptoms, or even colonize temporarily, furnishes one more example of the similarity of the behavior of amœbæ in man and lower animals; accordingly, it furnishes still further proof that the atypical amœbæ, just described, were the ætiologic factor in these cases, and that the symptoms obtained in kittens were not an artificial result of the special conditions under which the inoculations were made. For convenience, the cardinal features characteristic of these strains are presented in the following outline.

OUTLINE OF VARIOUS SPECIES AND STRAINS OF AMŒBÆ.<sup>1</sup>

Strain of amœbæ.	Morphology.		Parasitism.	Pathogenesis.	Virulence on passage.	Pathology.	Symptoms in man and animals.	Effect of emetine therapy.	Cultivability on agar.
	Character of nucleus.	Usual number of nuclei in cysts.							
Histolytica.	Chromatin poor.	4	+	+	Increases.	Ulcers.	Dysentery.	Good.	0
Coli.....	Chromatin poor.	8	+ <sup>2</sup>	J <sup>2</sup>	....	0	0	?	0
Limax.....	Chromatin rich.	1	0	0	....	0	0	....	+
Atypical strains.	Intermediate.	2 & 3	+	+	Increases.	Variable	Diarrhœa.	Poor.	0

<sup>1</sup> In order to express these factors in tabular form, it has been necessary to select only the cardinal features, and in the case of the atypical strains the data represent the more extreme examples. In addition to these four groups of amœbæ, it is distinctly possible that other types may exist which would represent intermediate stages in the process of evolution, such as the occurrence of a group capable of leading either a saprophytic or a parasitic existence.

<sup>2</sup> According to Schaudinn.

From this outline it is seen that these unidentified strains differ distinctly in their morphology, pathology, and pathogenic properties from both *E. histolytica* and *E. coli*. The morphology of the vegetative stage of these atypical strains is fairly characteristic and the variation from *E. histolytica* and



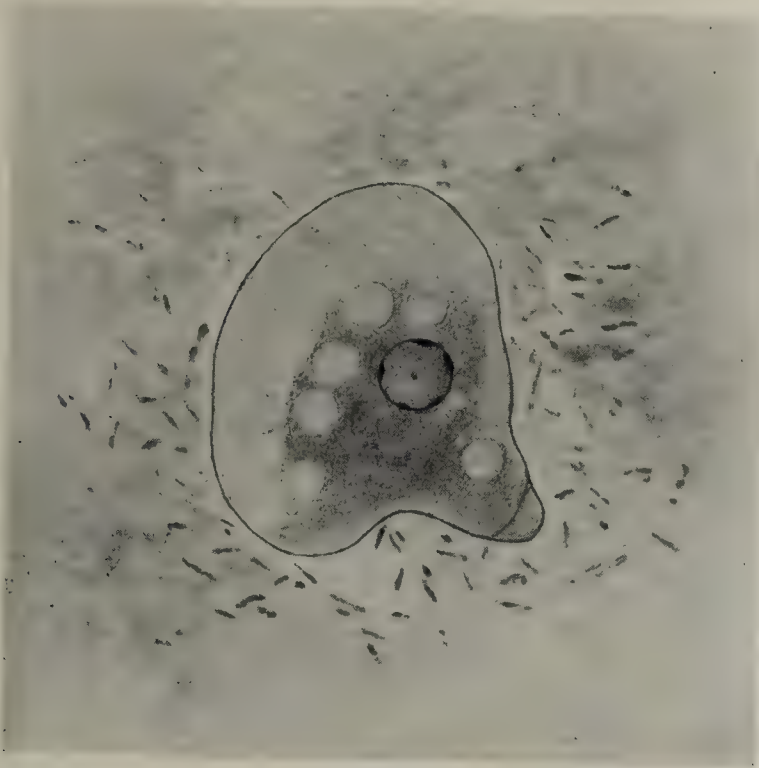


FIG. 1.

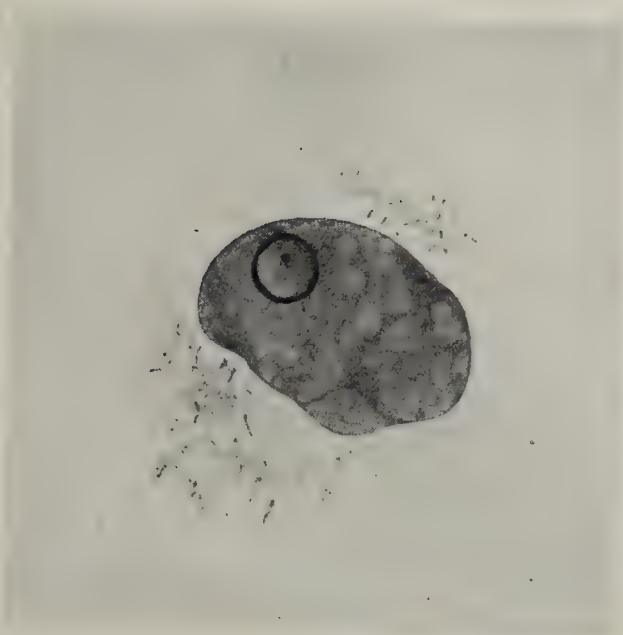


FIG. 2.

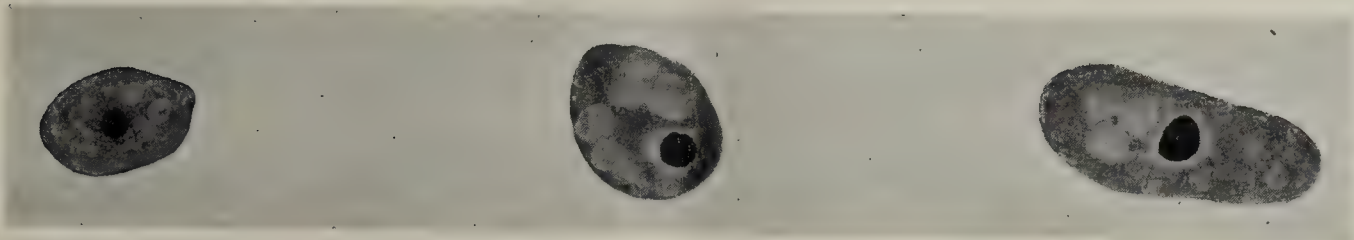


FIG. 3.

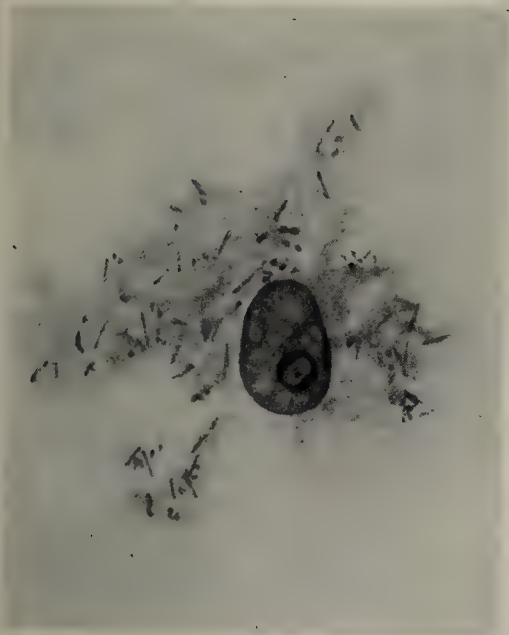


FIG. 4.

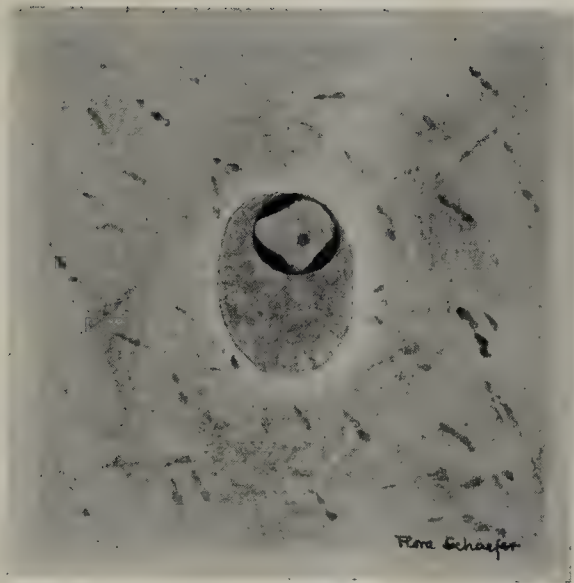


FIG. 5.



FIG. 6.

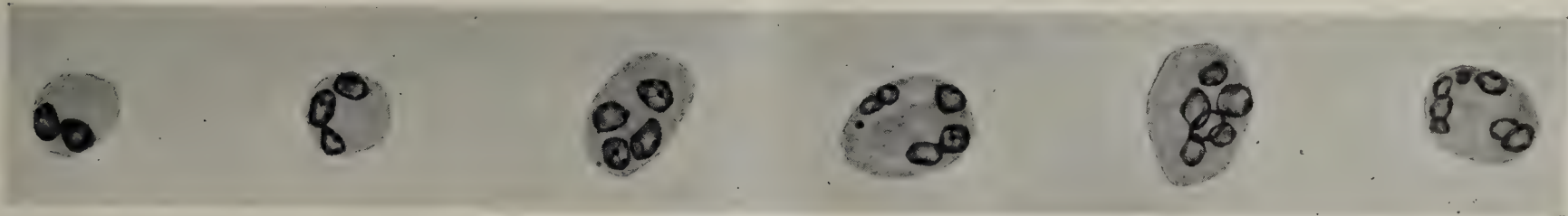


FIG. 7.



FIG. 8.







*E. coli* is much more marked than the differences between these two species themselves. Also in the method of forming the propagative stage, these strains of amœbæ differ from the two established types, since the predominant number of nuclei was only two and three, as compared with four and eight for *histolytica* and *coli*. In correlation with these differences in morphology, the clinical symptoms produced by these strains were at marked variance with those of typical dysentery. These differences in morphology and clinical symptoms were distinctly more marked than in other protozoan diseases in which separate species are recognized. For example, in the three types of Leishmaniasis the morphology of the parasites is so nearly identical that no constant differences are uniformly recognized by protozoologists; at least the species differentiation of *Leishmania donovani*, *L. infantum*, and *L. tropica* rests not upon differences in morphology, but upon the different effects produced by these parasites when acting in different parts of the body, their behavior upon animal inoculation and similar factors.\* Nevertheless, there are two features of importance in the preceding data which militate strongly against accepting these strains as altogether distinct from *histolytica*, when one considers the rigidity of the qualifications necessary for the establishment of a distinct species. In the first place even the most atypical of these cases (A) gave a fairly typical history of dysentery in the early years of his disease. Moreover, these three cases represent varying gradations between an extremely obscure form of diarrhœa on the one hand and the typical *histolytica* dysentery on the other. This is even more striking when some other mild cases of ordinary amœbic dysentery are considered, which were observed simultaneously with these.† Likewise, the morphology does not always conform to one extreme or the other, but in a series of cases all gradations are seen between the chromatin poor and the relatively chromatin rich nucleus. Furthermore, the features which characterized these atypical strains, although constant over a long period in a given patient, changed in a few months upon sub-inoculation in animals. Even in the most extreme case there were signs of increasing virulence accompanied by changes in morphology toward the *histolytica* type after a few passages through animals.

In view of these considerations it seems advisable to conclude that the virulence and other biological characteristics of *E. histolytica* are subject to some variation and that, with changes in environment, the morphological characteristics may vary. These variations occur both in the trophozoites and in the

\* The minor differences in the morphology of the *Leishmania* and the difference in clinical symptoms which they produce is certainly not more marked than in the case of *B. tuberculosis*; yet the difference between the lesions produced in the lungs as compared with those of lupus vulgaris, has never been suggested as a basis for differentiating various species of the tubercle bacillus. Recent work by Patton<sup>12</sup> in transmitting the parasite of kala azar to lower animals makes it possible that some of the supposed differences between *L. donovani* and *L. infantum* may be less rigid than has hitherto been supposed.

† These have been reported in brief in a previous number of the BULLETIN.

encysted stage. Features such as the amount of chromatin and its arrangement in the nucleus are not absolutely fixed characteristics, but are subject perhaps to more variation than has been suspected. A phenomenon that is even more surprising and important is the lability in the number of nuclei in the cysts. In these strains, developing under apparently unfavorable conditions, the mature number of four nuclei is not produced, but two- and three-nucleated cysts predominate.\* It was first observed by Hartmann<sup>5</sup> that *E. histolytica*, when infecting lower animals, undergoes, even in a short period of time, definite changes in morphology, resulting in the so-called "small generation," probably the *E. minuta* of Elmassian. It seems very natural, therefore, that the same phenomenon should develop in human infections. This observation by Hartmann offers further evidence in support of the view that these atypical strains of amœbæ have developed from *E. histolytica*. The clinical histories indicate that this development has taken place during the progress of the disease in a single individual; moreover, changes in the opposite direction can be brought about under experimental conditions resulting in a return from the atypical morphology toward the *histolytica* type. Therefore, there is not sufficient ground at present to classify these strains as a distinct variety of amœbæ, but we prefer to consider that they constitute merely a temporary alteration in *histolytica* which has been brought about by changes in environment.

Morphologically the trophozoites do not differ essentially from a new entamœba of man described by v. Prowazek,<sup>13</sup> *E. polecki*. However, the description of this amœba, like that of *E. testudinis*, a new species described by Hartmann,<sup>14</sup> is based upon the vegetative stage alone. The propagative stage is not described, and the trophozoites were not studied under changing conditions of environment such as would occur in tests for pathogenesis. Accordingly we do not feel that the description of *E. polecki* is sufficiently complete to enable one to recognize it with certainty, and we do not feel that there is sufficient ground as yet to establish *E. polecki* and *E. testudinis* as distinct species.

#### SUMMARY.

In the diagnosis of amœbic dysentery, it is ordinarily considered essential that the presence of *E. histolytica* be demonstrated in association with definite clinical symptoms. In three cases of obscure diarrhœa it was found that amœbæ were present in the intestine, which could not be identified morphologically with either *E. histolytica* or *E. coli*. Animal inoculation proved that these amœbæ were definitely pathogenic, the symptoms which characterized the disease in the patient appearing in the animals. After a careful consideration of the various factors involved in these cases, we feel that it is necessary to diagnose amœbic dysentery (intestinal amœbiasis) under conditions in which the clinical symptoms are

\* We realize, of course, that the rigid standards of bacteriology are not yet possible with amœbæ, and, like all work with amœbæ, these conclusions are open to the criticism that we may have been dealing with mixed infections; but the weight of evidence is against such an interpretation.



distinctly atypical and the amœbæ present vary markedly in their morphology from *E. histolytica*. Indeed, amœbic dysentery must sometimes be diagnosed in the absence of trophozoites and when only two- and three-nucleated cysts are present. A diagnosis under such conditions should be confirmed by the inoculation of animals.

As regards the systematic position of these strains, and their relation to *histolytica*, definite evidence was obtained that the amount of chromatin which characterizes the nucleus of *E. histolytica* may undergo fairly marked variation. Also the number of nuclei in the propagative stage has always been considered as being sufficiently constant to furnish a satisfactory basis for the differentiation of species. In these strains marked variation occurred in the number of nuclei in the cysts, sometimes only two and three being found, and under other conditions four and often five or six nuclei. Consequently we prefer to regard the strains of amœbæ occurring in these cases, not as a new variety, but as an atypical *histolytica* temporarily modified by environment.

For the present it seems permissible to recognize only two entamœbæ of man, namely *E. histolytica* and *E. coli*. We do not feel that *E. polecki* (v. Prowazek, 1912), found sometimes in man, or *E. testudinis* (Hartmann, 1910) of certain animals can be accepted as distinct species, in view of the limited information concerning the characteristics of the vegetative stage under changing conditions of environment, the absence of specific tests for pathogenesis in a susceptible host and the absence of information concerning the propagative stage.

This paper is the last of a series of four publications on amœbic dysentery, beginning in the June number of this BULLETIN in 1914. A brief summary of these has appeared in

a recent number of the *American Journal of Tropical Diseases and Preventive Medicine*. These studies have been conducted during the past year in the clinic of Professor Barker. It is a pleasure to express our appreciation to Dr. Barker for his interest in this work.

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#### ILLUSTRATIONS.

(Magnification  $\times 1500$ .)

- FIG. 1.—*E. histolytica*.  
 FIG. 2.—*E. coli*.  
 FIG. 3.—Group of three limax amœbæ from culture.  
 FIG. 4.—Atypical amœba found in patient A.  
 FIGS. 5 and 6.—Amœbæ from first passage of atypical strain A in animals.  
 FIG. 7.—Series of cysts showing varying number of nuclei in atypical strain from patient A.  
 FIG. 8.—Pus cell simulating an amœbic cyst.

## EXPERIENCES WITH THE PHENOLSULPHONEPHTHALEIN METHOD OF TESTING THE FUNCTION OF THE KIDNEY.<sup>1</sup>

BY OTTO HESS, M. D.

(From the Medical Clinic of the Cologne Academy for Practical Medicine. Director: Prof. Dr. Moritz.)

It is not my intention to give a lecture on the well-known methods of testing the function of the kidney, but merely a report of the results of 300 tests made by the Rowntree-Geraghty methods.

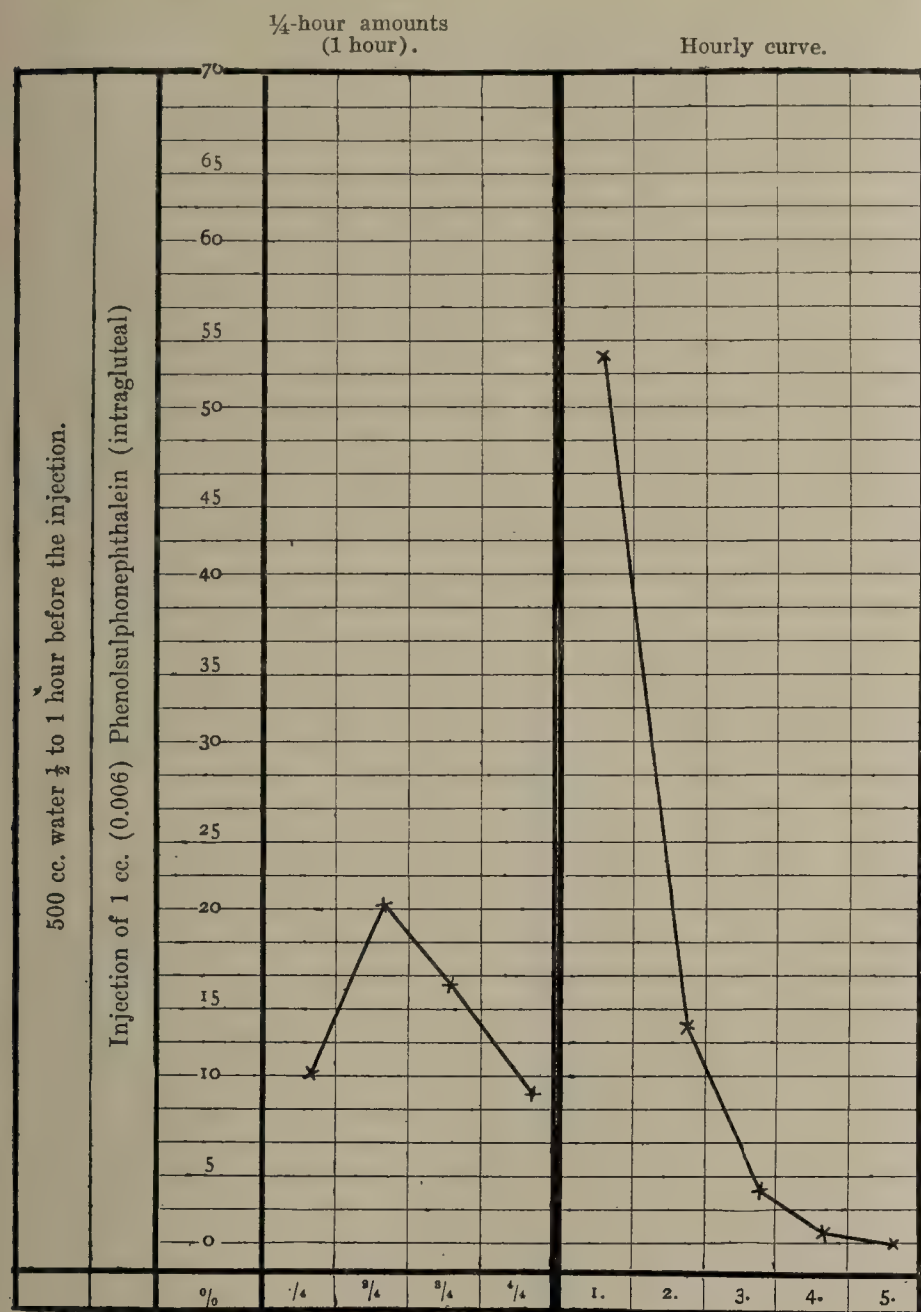
As has been previously noted by Rowntree and Geraghty, phthalein was found in the urine of healthy persons five to ten minutes after injection. After noting the time of the first appearance of the phthalein in the urine, hourly determinations were made by these authors. Under normal conditions the first positive reaction occurs almost constantly five minutes after injection, while in renal diseases the time of the first appearance of the phthalein may be delayed one hour or more. For this reason, observations were begun at the time of injection. Assuming that there is a difference in the excretion of

<sup>1</sup> An address delivered before the Rhine-Westphalian Society at Bonn, May 12, 1914.

the healthy and diseased kidney during the first hour, and in order to note the time of the first appearance of the phthalein, the urine was collected every 15 minutes during the first hour after injection. At the same time I hoped, by stating the normal curve for the first hour, to reduce the observation time of four hours, and thereby make the method more adaptable for the use of the private practitioner; but it is of considerable advantage to know the total excretion. There exists for the healthy kidney a typical curve of excretion for the first four 15-minute periods. Under normal conditions the quantity excreted during the first 15 minutes is a measurable amount, which increases during the second 15 minutes, rarely increases during the third, decreases during the fourth, and then steadily drops to zero. This has been noted in many observations made at regular 15-minute intervals. In making hourly estimations, the curve shows a large amount at first, a rapid



decrease in the second hour, and then a gradual decline until the test becomes negative.<sup>2</sup>



The curve represents the average of 100 normal cases.

PHENOLSULPHONPHTHALEIN CHART.

Before discussing the results of the test in disease, it is well to note that even normal kidneys may show certain variations in excretion. As previously noted,<sup>3</sup> I have frequently obtained in the same patient a more rapid and complete phthalein excretion in the afternoon than in the forenoon. This may be attributed to stimulation caused by the ingestion of food, since phthalein itself does not stimulate the action of the kidneys. It is important to remember that these variations are not observed in renal diseases.<sup>4</sup> Furthermore, decreased amounts of phthalein are excreted by apparently healthy kidneys, which may be due to a decreased urinary output or some pathological

<sup>2</sup> At the suggestion of Professor Moritz a chart was arranged to show the normal average curve of phthalein excretion in 100 cases. This chart, of which the one that appears here is a modification, also contains space for notes regarding the condition of the heart and kidneys. The full chart, with a detailed description of the method, can be obtained from F. Hellige & Co., Freiburg, in Breisgau.

<sup>3</sup> Hess: Muench. med. Wchnschr., 1914, Nr. 51.

<sup>4</sup> Further researches on the effects of the phthalein test are not included.

changes in the urogenital system. Occasionally cases are noted which, though quite normal, show a variation in the amount of phthalein excreted without any diminution in the amount of urine. These are, however, rare exceptions.

Regarding the reliability of the test in diseases of the kidney, I have found, in every case of kidney disease confirmed by autopsy or operation, an abnormal phthalein excretion closely parallel to the severity of the condition. The most striking results were obtained in the various forms of chronic nephritis. The time of the first appearance of the phthalein is delayed and the amount excreted diminished, or the curve is abnormal. In most cases the duration of the excretion is prolonged. The more severe the disease, the greater is the deviation from normal. Dietsch and others state definitely that there is a parallelism. Rowntree and Geraghty describe several cases in which they were able to predict an uræmia solely from the abnormal phthalein excretion. My own observations allow me to say that all cases showing an abnormally low or an entirely absent excretion allow of a very bad prognosis. Repeated tests during the course of treatment enable one to decide whether the treatment is beneficial or whether the nephritis is incapable of any improvement.

One great advantage of this method is the possibility of diagnosing nephritis without any previous dietary preparation in many cases which are clinically doubtful. These are the patients who complain of slight cardiac distress and frequent headache. They generally have a high blood-pressure and a slight cardiac enlargement, but the urine presents nothing abnormal. We know that these patients suffer from chronic nephritis, but the phthalein test is the only one to quickly confirm this fact. Daily examinations of the urine occasionally show slight traces of albumin and sometimes a few casts.

In acute diseases of the kidney, in toxic derangements thereof and amyloid kidney, the results of the phenolsulphonphthalein test are not so clear, and occasionally quite contradictory. Cases of acute renal disease often show a relatively good excretion of phthalein despite severe clinical symptoms (albumin, cellular elements in abundance, and œdema). As these patients improve, the excretion of the phthalein rapidly becomes normal. On the other hand, there are patients with clinically these same symptoms and a comparatively good phthalein excretion, but as they clinically improve, the phthalein excretion gradually grows more abnormal, and the excretion of NaCl and the diastase content decrease at the same time and in the same degree. There we see an acute disease of the kidney gradually grow to be one of a chronic type with permanent tissue changes.

In other forms of kidney disease the excretion varies with the severity of the condition. In uncomplicated amyloid disease the excretion appears to be practically normal, but there are a few cases where the excretion of phthalein does not quite parallel the renal changes. These require further investigation.

In applying the Rowntree-Geraghty test it is always necessary to take into consideration extra-renal influences, especially those from the heart. In cases of cardiac insufficiency the phthalein excretion is delayed, which may be attributed to



delayed absorption of the phthalein. In cases where cardiac weakness is responsible for the kidney affection, the excretion of phthalein increases and becomes normal as the cardiac condition improves. In croupous pneumonia we often find that the excretion of phthalein is subnormal, being parallel with the NaCl retention. As soon as the crisis is over, it returns to normal unless there is some chronic renal disease in addition to the pneumonia.

The phthalein excretion is abnormal in all cases where sodium chloride and urea or one of them is not excreted in a normal amount. Investigations recently made in our clinic by Herr Caan,<sup>5</sup> have also shown that in almost all cases there is a parallelism between the diastase content of the urine and the phthalein excretion. In chronic nephritis, the importance of this observation is very striking.

From these facts a most important conclusion, especially for general practice, may be deduced. It may be assumed that whenever the excretion of phthalein is abnormal, the excretion of NaCl and of nitrogen by the kidneys is also deficient, and that this simple test might take the place of the more difficult sodium chloride test, although for clinical purposes the NaCl and other tests are of great importance. It must be remembered that the addition of 10 gm. of NaCl to the diet of a patient suffering from nephritis may produce unfavorable symptoms almost uræmic in character. Consenz<sup>6</sup> also considers this a dangerous procedure.

In conclusion, let us consider briefly the phenolsulphone-

<sup>5</sup> Will appear shortly in *Deutsch. Arch. f. klin. Med.*

<sup>6</sup> Consenz: *Arch. f. klin. Med.*, Bd. 108, S. 353.

phthalein test in renal diseases other than nephritis. My cases of unilateral renal disease, nephrolithiasis, pyonephrosis, etc., some of them confirmed by operation, show that the phthalein test is valuable for determining the amount of work each kidney is capable of doing. It is superior to other color tests in the accuracy of the information it yields. The result of the phthalein test shows how much of the parenchyma is involved, and is of much value in the differential diagnosis of doubtful renal tumors. The Rowntree-Geraghty test is regarded with favor by most observers, but in some published cases where subnormal amounts were excreted from apparently healthy kidneys, previous mention is made of the existence of tumors, pregnancy, etc. Ware has recently published a paper, of which I have only been able to obtain an abstract, in which he claims that the phthalein test is worthless. My investigations do not confirm his opinion. Although there may be some cases with severe clinical symptoms in which the test unexpectedly shows good renal function, we are nevertheless justified in concluding that the phthalein test surpasses all other similar methods by its simplicity. It can be applied immediately without any dietary preparation, and can be used in all cases, even uræmic conditions. The result is rapidly obtained, and is of value both for diagnosis and prognosis. The parallelism between the excretion of phthalein, NaCl and nitrogen is of great importance, and diet and treatment may be prescribed from the results of the Rowntree-Geraghty test alone in cases which could not be recognized as chronic nephritis by the clinical methods hitherto available. A more extensive article on this subject will be published in the *Muenchener medizinischer Wochenschrift*.

## PROCEEDINGS OF SOCIETIES.

### THE JOHNS HOPKINS HOSPITAL MEDICAL SOCIETY.

DECEMBER 7, 1914.

#### An Operation for Hypophyseal Tumors. Exhibition of Case.\*

DR. G. J. HEUER.

Dr. Heuer described an operation for attacking lesions of the hypophysis, and presented a patient upon whom this operation had been done. He discussed the various methods of approaching hypophyseal lesions and noted their disadvantages and their impracticability in permitting a thorough operation. These operations include the transphenoidal operation as employed by Hirsch, Cushing and others and the intracranial operations of Krause, McArthur, Fraser and Killiani. The advantages of the operation as proposed are a very much more extensive view of the entire chiasmal region, and even, to a certain extent, of the region behind the chiasm. Both carotid arteries are easily exposed and the entire field is under control. The operation as described consists of a large, low, frontal osteoplastic flap. Following this, the dura is opened almost as widely as the bone defect. Lumbar puncture is then done, the head tilted backward and, by gravity, the frontal lobe falls away. Further exposure is obtained by retraction with the spatula, which is introduced laterally, *i. e.*, just in front of the temporal lobe. In two cases this method was employed and in each instance the results were most satisfactory.

\* To be published in full later.

The first case was presented at the meeting. The patient was a boy, aged 10, who had had complete blindness in one eye, hemianopsia in the other and a gradually increasing headache. There was also involvement of the third and fourth nerves, as indicated by complete ptosis on the right side and a wide inert pupil with absence of all reaction. The X-ray showed a greatly enlarged sella turcica. The discs showed pallor, indicating optic atrophy. There were no glandular symptoms referable to the hypophysis. At operation a large, bluish cyst protruded above and between the optic nerves. This was opened and a large amount of blood-stained fluid evacuated. The patient's recovery was very satisfactory, as vision returned almost entirely. All the palsies disappeared and he remained well for about six months, when the symptoms gradually returned. He is now in practically the identical condition in which he was on the first admission. In addition, he has grown fat.

The second patient was a girl, aged 19, with blindness in one eye and almost complete loss of vision in the other. There was some adiposity, increased sugar tolerance, intermittent polyuria and sexual disturbances. The sella turcica appeared normal in the X-ray. It was evident that the tumor was of supra-sellar origin and could not be attacked by the transphenoidal route. At the operation, as described above, a cyst was found behind the optic chiasm, probably arising in the infundibulum, although its exact origin could not be determined.



**Complement Fixation in Thyroid Diseases.\*** DR. S. R. MILLER.

The tendency in recent times to devise functional tests for the various glandular organs of the body, has now come to embrace the so-called ductless glands, about which there is so much of interest at present. The frequency of thyroid conditions, and especially of states of hyperthyroidism, makes it desirable that functional tests for the activity of the thyroid gland be available, especially for the diagnosis of border line cases. This need was called attention to by Dr. Barker in 1914; he mentioned that there were at that time four tests of this nature, namely, Reid Hunt's acetonitrile test, tests for hyperadrenalinemia, Abderhalden's dialysis test, and finally the complement deviation test of Roseo. For numerous reasons, it was decided to try out the last-named test. For the purpose of antigens various extracts were prepared from thyroid tissue removed at operation in cases of Graves' disease. After submitting the various extracts to suitable titrations the sera of a number of patients suffering from Graves' disease, other thyroid conditions, unexplained tachycardias, dementia præcox, and known cases of lues, were submitted to complement deviation tests, according to the well-known method of the Wassermann reaction. The results in a series of cases were remarkably negative, even when each serum was tested against a total of 19 or 21 different antigens. No positive findings in any thyroid conditions were observed. The only sera which gave complement fixation were those from cases of known lues, which showed a positive Wassermann reaction as tested in the usual manner. Similar positive results were secured when spinal fluids from cases of general paresis were employed. It would seem, therefore, that the test of Roseo is of no clinical value in the diagnosis of thyroid conditions.

**The Results of the X-Ray Treatment of the Thymus Gland in Graves' Disease. (Abstract.)** DR. W. S. HALSTED.

In an address before the New York Academy of Medicine last year (March 14, 1914), I called the attention of American physicians to the fact that the thymus gland may play an important rôle in Graves' disease.†

My remarks tonight are intended as a continuation of the address referred to, which was published last August in THE JOHNS HOPKINS HOSPITAL BULLETIN. It may be assumed that very few of our audience this evening read the midsummer numbers of medical journals, and hence, in order to make intelligible the special facts which I desire to emphasize at this time I shall make an occasional draft upon my previous paper.

Less than four and one half years ago Meltzer ‡ made the following cautious statement concerning the thymus gland: "With our present knowledge of the importance of the other ductless glands we are hardly justified in assuming that the thymus is a worthless fetal remnant. But we have to acknowledge that as yet there are no reliable observations or experiments which indicate clearly that the thymus has a function in postuterine life."

My interest in the thymus was greatly stimulated by the report of Garré in 1911, at the Fortieth Congress of the Deutsche Gesellschaft für Chirurgie, of a case in which he had primarily removed the thymus for the cure of Graves' disease. Although well aware of the fact that a persistent or revived thymus had repeatedly been observed in Basedow he was astonished to learn from the statistics obtained by his assistant, Dr. Capelle, that a thymus persists hyperplastica had been found in 95 per cent of the fatal cases,

\* This article is to be published in full in a later number of THE JOHNS HOPKINS BULLETIN.

† Harvey Lecture. The Significance of the Thymus Gland in Graves' Disease. March 14, 1914.

‡ Meltzer: Animal Experimentation in Relation to Our Knowledge of Secretions, Especially Internal Secretions. Proc. of the Path. Soc. of Phila., 1910.

whether death was due simply to the severity of the disease, or occurred during the operation, or within 24 hours after the strumectomy.

Selecting a florid example of Graves' disease for his experiment he excised the thymus without molesting the thyroid. The result in this, his first case, was as follows: "Clinically no definite influence on the struma, the exophthalmos or the eye symptoms, but an unequivocal improvement in the general condition as expressed by the signal quieting of the heart's action, rapid increase in weight, and a complete regression of the Kocher blood-picture, the lymphocytes falling from 40 to 25 and then to 10 per cent." Prof. Garré gave to his assistant, Dr. Capelle, credit for the work and for the thought which led them both to these conclusions, which, he said, find essential support in the proof by Klose that in the thymus substance there is a heart poison. Aside from the special action of the thymus there exist certainly, said Garré, important reciprocal relations between these two glands. Reasons for this view are given in my Harvey Lecture.

In the three and a half years which have elapsed since Prof. Garré's report, research work on the thymus, which already had been considerable, has assumed large proportions, and the interest of surgeons and also of physicians, particularly in Germany, Russia, Switzerland and Italy, in the possible part that the thymus may play in Graves' disease has been thoroughly aroused. I am hoping each day that there may appear from our country a contribution to the subject. Up to the present time I have seen no reference made to it in the American or English literature. Operative confirmation of the correctness of the view of Garré and Capelle and, I should add, of Hart and Rehn and Klose and Sauerbrück and others is given in two papers by von Haberer.\* Most convincing is the report of case 3 in von Haberer's first paper.†

For a fuller consideration of the operative side of the question, I must again refer you to my paper.

To-night we are concerned simply with the results of the X-ray treatment of the thymus in Graves' disease. Rudberg, Aubertin and Bordet, Pigache and Bécclère, Arella, Heincke, Peters, Klose and others have shown that under the influence of the X-ray the thymus rapidly undergoes involution, an involution which is so extensive that Klose expressly warns against radiation of the thymus region in children. Heeding this warning I excised portions of the thymus in two cases of Graves' disease in children, fearing to submit them to the risk of the X-ray treatment. In my paper (pp. 231 and 232), to which for the sake of brevity I have had occasion to refer so frequently, a brief reference is made to the result which followed treatment by radium ‡ of a patient upon whom in two stages a double thyroid lobectomy had been performed about two years previously. The effect of this treatment was so astonishing that I promptly wrote and telegraphed to six selected patients, those in whom the improvement after double thyroid lobectomy had been particularly unsatisfactory, urging them to return to the hospital as soon as possible. All of these patients responded promptly to my call, one coming from as far as Texas, making a journey which required four days. I wish here to express my gratitude to these patients, and my indebtedness to Dr. Baetjer and to Dr. Waters who have given the X-ray treatments to these six cases of double lobectomy and indeed to all of my new and to many of my old patients with Graves' disease.

As nearly a year has passed since this treatment was first tested I feel that we may now with considerable assurance speak of the results.

\* von Haberer: Mitt. a. d. Grenzgeb. d. Med. u. Chir., 1913, Bd. 27, S. 199. Arch. f. klin. Chir., 1914, Bd. 105, S. 296.

† An abstract of this case as it appears in the August number of the BULLETIN was read by Dr. Halsted.

‡ The radium treatment was very kindly given to this patient by Dr. Burnam in the sanatorium of Dr. Kelly.



In the six cases in which after double lobectomy the result was unsatisfactory the X-ray treatment was begun in March, April or May, 1914. The time elapsed between the surgical operations and the treatment by radiation was  $4\frac{1}{2}$  years (one case), 3 years (one case), 2 years (one case), 1 year (one case), 10 months (one case), 6 months (one case).

Four of these cases were so ill on admission that ligation of the thyroid arteries was done in two or more stages preliminary to the first lobectomy. In two cases the four arteries were tied before excision was ventured. All of the patients were greatly improved by the operations and from being bedridden and in a pitiful state were enabled to go about moderately and find some pleasure in existence. But in none was the result satisfactory to myself, although four of the six cases were more than content with the relief which they had obtained from the operations. In only one case was there perfectly definite retrosternal dulness and X-ray shadow.

In each case the result of the radiation was prompt and striking. The improvement was so great that without exception the patients expressed delight at the result. Two state that they are "perfectly well." Two young women, and the youngest of the six, who were greatly discouraged by the inadequate operative relief, have now, with occasional exceptions, a normal pulse and enjoy life almost to the full; one, however, is still concerned about the incomplete subsidence of the exophthalmos which was extreme, and the other is easily fatigued. Each of the cases presents features of special interest which I hope to record at some other time. For example, in one pigmentation and in two the yellow pasty hue of the skin disappeared after the X-ray treatment.

In two, pronounced eye signs were improved almost immediately.

In three, headache, which had been more or less constant, was the first symptom to vanish and has not returned.

Asthenia, which was common to all the cases, has been particularly influenced.

In one, pronounced agoraphobia has seemingly been cured. This patient who formerly dreaded crossing a street now threads crowded thoroughfares without concern.

It is interesting to note that in no instance did the lobectomies fail ultimately to restore the blood-picture, to reduce the percentage of lymphocytes when this had been too high. This was hardly to have been expected in cases so definitely relieved by radiation of the thymus as to indicate persisting overactivity of this gland.

I quite agree with Prof. Kocher and Dr. Albert Kocher that strumectomy in Graves' disease restores after a time the normal blood-picture and that, therefore, in case the thymus is responsible for the high lymphocytosis, excision of the thyroid must correct in this respect the overactivity of the former gland.

But the fact that after double lobectomy without adequate relief, radiation of the thymus was followed by great improvement would indicate that the thymus was still uncontrolled, and this being the case, suggest that the high lymphocytosis may not have been caused solely by the thymus.

Is it conceivable that the persistent cells of the complex thymus, those causing the symptoms which were relieved by Roentgenization, may not be the ones which gave rise or give rise to the lymphocytosis; or that with the degeneration and waning power of the cells their ability to sustain the lymphocytosis may be lost while they may still be responsible for the unrelieved symptoms? On the other hand, can we be sure that there is not sufficient diffusion of the rays aimed at the thymus to affect the remains of the thyroid lobes? This suggestion is scouted by the radiologists.

I have in mind a case of double lobectomy in which a tiny fragment of the isthmus of the thyroid became greatly hypertrophied after the operations, and disappeared entirely 48 hours after treatment of the thymus by radium.

Of very especial interest to me are the conclusions given by Dr. Albert Kocher of Bern in an admirable paper, Ueber Base-

dow'sche Krankheit und Thymus, which he presented at the meeting in Berlin last April of the Deutsche Gesellschaft für Chirurgie. Dr. Kocher's views have, undoubtedly, the endorsement of his father, Prof. Theodor Kocher.

They are as follows:

"Basedow's disease without hyperplasia of the thyroid gland has not as yet been proved at autopsy or by operation.

On the other hand, a considerable number of typical Basedow cases, with all the characteristic symptoms, have been observed in which no histopathological alteration of the thymus was found.

It is, however, remarkable that in quite a large number of the Basedow patients there is found a late hyperplasia or late involution of the thymus. We estimate the number of these, on the basis of clinical and anatomical findings, at 45 to 50 per cent of all Basedow cases.

The thymus-hyperplasia is much more common in the young than in the old Basedow patients. The age of most frequent occurrence of thymus-hyperplasia does not correspond with that of the commonest age for Basedow.

From the weight alone of the thymus no conclusion can be drawn as to the amount of thymus-parenchyma which may be present.

In the great majority of cases of Basedow with combined thymus-hyperplasia there is only a moderate enlargement of the thymus (15 to 30 grams). It is rare to find in them a gland weighing 50 grams. Equally heavy thymus glands occur without Basedow.

The histological examination of our Basedow-thymus glands by Pettavel as well as those of von Haberer has shown that, without exception, there has been a mixed hyperplasia of cortex and medulla, and that histologically no difference existed between the hyperplasia of childhood and that of Basedow.

In 21.5 per cent of the Basedow-thymus glands there are definite signs of an age-involution with abnormal amount of parenchyma; in 14.2 per cent distinct indications of pathological involution with excessive parenchyma-mass.

Thymus-hyperplasia is much more common in some regions than in others, also in certain families, in which it occurs with and without Basedow. The examinations which have hitherto been made, especially the anatomical, make it probable that we are dealing with a regionary family persistence, or late hyperplasia and late involution established upon a congenital or, if you will, constitutional base.

Clinical observations suggest that, at least in certain instances, there supervenes with the Basedow a further hyperplasia or revival, a regeneration in other words, of thymus-parenchyma, which, with the cure of the Basedow, for the most part disappears. That there is such a revivification or regeneration we can only surmise, for we have up to the present time no anatomical proof of it in man.

Accordingly, hyperplasia of the thymus would be present, for the most part, before the Basedow and could not, therefore, be the direct cause of the disease, especially as we find the same hyperplasia present in individuals who have at no time in their lives suffered from Basedow.

The cause of the thymus-hyperplasia might stand in direct relation to the hypoplasia of the medulla of the adrenals.

In accordance with biological laws it is certainly rather to be assumed that an organ is congenitally hypoplastic and in consequence another hypertrophies, than that congenital hyperplasia of one organ is responsible for hypoplasia of another.

Hypoplasia of the adrenal-medulla in Basedow's disease was first demonstrated on our material by Pettavel; it is found with and without thymus-hyperplasia. In Basedow there occurs a cellular hypertrophy in the hypoplastic suprarenal-medulla.

Both of the changes, adrenal-hypoplasia and thymus-hyperplasia, remain latent in most cases until the onset of the Basedow, wherein, by the altered function of the thyroid, there is called forth a disturbance in compensation.

Up to the present moment it cannot definitely be said whether



we may attribute certain of the symptoms of Basedow's disease to changes in the adrenals and the thymus, or whether we may do so only in certain cases.

As proof that the adrenal-hypoplasia was present in latent form before the manifestation of Basedow we regard the appearance and disappearance of certain symptoms synchronously with the vanishing of the Basedow, symptoms which one observes in cases of atrophy of the adrenals without Basedow; we mention only the melanoderma of certain Basedow patients.

Something similar may exist for the thymus-hyperplasia. We have, therefore, emphasized the above symptoms as occurring in Basedow with thymus.

To this extent can one speak of a special action of the thymus and adrenals and of special symptoms attributable to the influence of these organs in Basedow's disease.

For the view that a typical Basedow picture, without thyroid hyperplasia, can be evoked by the hyperplastic thymus we have up to the present moment no support.

For the therapy of the cases of Basedow complicated with thymus-hyperplasia, the following conclusions present themselves:

In these cases, also, the disease is recovered from by sufficient reduction of the hyperplastic thyroid, provided operation is not too long deferred. The thymus-hyperplasia then gradually regresses.

The thyroid operation is in these cases not more dangerous than in the Basedow patients without thymus.

Basedow with a high degree of thymus-hyperplasia, as is more frequently observed in younger individuals, is cured only by earliest possible operation upon the thyroid gland.

In these cases, as also in those in which obdurate symptoms persist, and further when there is a tendency to recurrence, thymectomy may with advantage be added to the thyroid excision.

The indication for thymectomy in Basedow's disease may be determined not only by the existence and severity of certain symptoms but also by the result of the test-administration of preparations of the thymus and thyroid glands. A preliminary treatment, before the thyroid operation, with thymus preparations and with Roentgen-radiation of the thymus is indicated in cases which react favorably to these procedures. Such treatment is, however, only temporary in its effect; especially is this true of the radiation, and it must therefore be undertaken only a short time prior to the operation upon the thyroid gland."

Dr. Kocher's opinion that the effect of the X-ray in cases of Graves' disease is transient might seem, at first thought, not to accord with our experience. But our views do not necessarily conflict. In Professor Kocher's clinic the Roentgenization of the thymus was done before the strumectomy, whereas in our six cases of double lobectomy it was after the final operation upon the thyroid—in one case  $4\frac{1}{2}$  years thereafter. We believe with Dr. Kocher that there is probably a regression of the hyperplasia of the thymus after strumectomy. Granting this, it is presumable that the Roentgenization of a gland (the thymus) at a time when there is a continuous tendency to degenerate should be more effective and more permanent in its results than in the period of its greatest activity, particularly when this hyperactivity is being constantly sustained by the stimulation of another organ (the thyroid gland).

#### Roentgen Technique in the Treatment of the Thymus Gland in Graves' Disease. DR. C. A. WATERS.

The technique employed in the treatment of Graves' disease by Roentgenization of the thymus gland has been uniform throughout and the observations have been made from sixty cases. Different types of cases and different stages of the disease have been dealt with, as related by Dr. Halsted.

The treatments were divided into three series, with intervals varying from two to three weeks between irradiations. Six treatments were given in each series, over the anterior chest wall starting in the first interspace on the right side close to the sternal

margin, through a portal of entry 5 cm. in diameter. Irradiations were given in the majority of cases on six successive days in the first, second and third intercostal interspaces along the right and left sternal margin; however, a number of the patients received six treatments at one seance. The patients were then allowed to wait until two weeks had elapsed after the last treatment before beginning the second series of irradiations.

They were again treated in the same manner as before, and a like interval of time allowed, before receiving the third or final series; therefore, no cases have received more than three series, or eighteen treatments, and some only one and two series comprising six and twelve treatments respectively. Each individual irradiation consisted of a six-minute exposure, given through a 1 mm. aluminum filter at a focal and pastille distance of 20 cm. We have used the full pastille distance, that is, the same as the focal distance; and contrary to the general rule of inverse proportions of multiplying by the square of the inverse of one-half the distance, which would be four, we have multiplied the skin dose (3 H) by  $2\frac{1}{2}$ ; thus we have given a dose of  $7\frac{1}{2}$  H units through each portal of entry, at each sitting; this constituting the erythema dose. So each area received the erythema dose,  $7\frac{1}{2}$  H, three times or  $22\frac{1}{2}$  H, the six areas receiving a total dose of 135 H.

The Holzknecht, Sabourand-Noire and Benoist radiometric systems were employed throughout the work, and the unexposed parts of the body were covered with a 1 mm. lead sheet, the chest wall being reinforced by a 3 mm. lead protector.

A parallel spark-gap of seven inches, tungsten target and coolidge tubes with 5-7 milliamperes of current were used.

In the sixty cases treated only one atypical reaction occurred, a brilliant blush coming on thirty minutes after receiving the last dose of the third series and lasting as such for six weeks, gradually fading away with no vesiculation or other ill effects.

The normal skin reaction after Roentgenization in the manner described consists of a definite faint blush, which appears in from one-half hour to six hours after irradiation, usually lasting from one to two weeks, gradually fading away followed by slight pigmentation, which by the end of three weeks has also entirely disappeared.

#### Some Medical Aspects of Hyperthyroidism. (Abstract.) DR. L. F. BARKER.

Though papers of importance upon pathological conditions of the thyroid have appeared, there has been but little new published during the past year bearing upon the functions of the normal thyroid. One of the most interesting reviews of the newer work recently published is that of F. Kraus, who presented the subject at the International Congress in London (1913). He emphasized an idea which has been growing among clinicians, namely, that the hormonal substances produced by the thyroid gland influence electively the continuous-tonic innervations in the domain of the vegetative nervous system, and also the autochthonous vital processes of the tissues themselves. That is to say, it is believed that the thyroid hormones may influence directly the actual cell life, independently of, as well as through the intermediation of, innervations. It is even possible that the particular influence of the thyroid on metabolism may concern the autochthonous processes of the tissue cells directly.

The idea that Graves' disease is not merely a hyperthyreosis but is also a dysthyreosis seems to gain support. In other words, the condition is not due simply to an overactivity of a hypertrophic normal gland, but is the result of an actual perversion of secretion in a pathologically altered gland.

Dr. Halsted has spoken of the reciprocal relations of the thyroid and the thymus. Certainly, the newer studies indicate that a large number of patients suffering from Graves' disease are also "thymus carriers"—at least 50 per cent of the severer cases. In nearly



all of the fatal cases examined, an enlarged thymus has been found at autopsy.

Several papers have dealt with the vagotonic and sympathicotonic phenomena in Graves' disease (Eppinger and Hess, C. von Noorden, Jr., Barker and Sladen, and others). In our experience here, and this I think is the general experience elsewhere, most of the cases are "mixed," there being nearly always symptoms that are "vagotonic" along with symptoms that are "sympathicotonic" in the same patient. This appears to be true, especially of the patients with marked nervous and mental disturbances. The symptoms, it is true, are in some patients predominantly vagotonic in type, while in others they are predominantly sympathicotonic. In the interesting paper of Capelle and Bayer, to which Dr. Halsted has referred, an attempt has been made to establish a histological basis for both the sympathicotonic and the vagotonic influences, not only in the thyroid gland, but in the thymus as well.

The clinical difficulty of telling whether the thymus is actually enlarged or not is sometimes a very real one. If there be dulness on percussion to the left of the manubrium, or if Boggs' sign be positive, enlargement is probable. Roentgenograms are helpful in deciding whether or not the thymus is enlarged, as is also the so-called Kocher blood-picture (relative lymphocytosis).

Despite the prevalent opinion that thymotoxic influences are added to thyreotoxic injury in Graves' disease, there are still two camps among clinicians, one urging that the symptoms are due to too much thymus-activity, and the other asserting that they are due to thymus-deficiency. Thus we find reports of wonderful cures produced by feeding thymus extract on the one hand (R. Hirsch), though, on the other, good results have followed surgical extirpation of the thymus (v. Haberer, Klose), and exposures of the gland to X-ray influences.

The enlarged thymus of children with status thymicus is now frequently treated by X-rays (Sidney Lange), and the X-ray treatment of the thymus in Basedow's disease has, as Dr. Halsted has pointed out, begun to appeal to clinical men. In December, 1913, E. Stoerk made a report to the Society for Internal Medicine and Pediatrics in Vienna. In a report by Sinozersky (July, 1914) on 20 patients suffering from Basedow's disease treated with Roentgen-rays over the thymus, giving a course of four to six treatments at intervals of three or four days, a second series of exposures being entered upon at the end of three weeks, the author states that the results were so striking that he feels that the rôle of the thymus gland in the pathogenesis of exophthalmic goiter is now established beyond question. He states that under X-ray exposures, directed against the thymus, the pulse fell from 120 or 140 to 80, the other cardinal symptoms of the disease abated, and the differential formula of the white blood corpuscles became more nearly normal.

An interesting statistical article on the course of Basedow's disease has been published by Dr. Plummer of the Mayo Clinic. In the experience of that clinic, Graves' disease usually begins acutely, and reaches its acme in the second half year. The disease continues, with intermissions and exacerbations, for about four years, but not much longer. Ordinarily, cerebral irritation, vasomotor disturbances of the skin, tremor, nervous irritability, tachycardia, asthenia, myocardial insufficiency, exophthalmos, diarrhoea, vomiting, psychic depression, and icterus occur in serial sequence. The toxic phenomena and non-hyperplastic goiter tend to set in on the average about fourteen years after the development of the struma and involve predominantly either the circulatory system or the structures, abnormalities of which give rise to a picture similar to Graves' disease. Plummer postulates three toxic elements of the thyroid secretion. One injures especially the nervous system, another the circulatory apparatus, and a third causes the exophthalmos. In outspoken exophthalmic goiter, it is the element which injures the nervous system which is produced in largest amount. Very careful studies of the pathology of the thyroid gland in exophthalmic goiter were published last year from the same

clinic by Dr. L. B. Wilson, and Drs. Blackford and Sandford believe that they have demonstrated the presence of a depressor substance in the serum of the blood of patients affected with this disease. The intensity of the depressor effect was proportional to the acuteness of the intoxication. In their opinion this depressor substance is neither cholin nor any ordinary peptone.

On the other hand, Kraus asserts that Retzlaff has proven that the adrenalin content of the blood is increased in exophthalmic goiter. Gley and others, like Blackford and Sandford, state that they have demonstrated conclusively that blood serum and extracts of the gland have a depressing effect, and that the blood must contain hypotensin.

As to the treatment of exophthalmic goiter, most surgeons advise operation whenever the diagnosis is definite. The majority of medical men advocate, first, conservative treatment—rest, hydrotherapy, thorough upbuilding, arsenic to slow metabolism, etc., until it is possible to see whether the patient will respond and make surgical intervention unnecessary. Some surgeons also adopt this view. Surgeons see chiefly the classic examples—outspoken cases of Basedow's disease; medical men see every transition from normal function to the outspoken Basedowian syndrome, and I think are likely to make the diagnosis of Graves' disease at an earlier stage than was formerly possible. It is surprising how rapidly some patients improve under medical treatment. Indeed, after two or three days of suitable measures there is sometimes a remarkable amelioration of the symptoms. In many instances, however, improvement is so slight that we do well to advise prompt surgical treatment.

I, too, have been interested recently in watching the effects of Roentgen-ray treatment of the thymus in some of the cases here. Some have improved markedly. Others have not, as far as I can see, improved; some have told me they were worse after the treatment. I believe that we have to deal here with another instance of a common experience in the treatment of Basedow's disease, namely, that a therapeutic measure valuable in some cases, is not helpful in all. We have not found any one thing yet that is wholly satisfactory in the treatment of all cases of Basedow's disease, but we must not fail to be grateful if in the X-ray applied over the thymus we have an agent which will help us in some cases not benefited by the remedies hitherto used.

#### DISCUSSION.

DR. JANEWAY: I confess it seems to me that on this question of what one shall infer from the beneficial results of any therapeutic measure in relation to exophthalmic goiter, the wisest words ever said were those of Epictetus in his First Discourse: "The beginning of philosophy is the observation how men contradict each other, the search whence cometh this contradiction and the censure and mistrust of bare opinion."

Beyond that statement I do not think we are any of us in a position to go at the present moment in regard to the treatment of this disease.

I agree with Dr. Barker as to the frequency of improvement and permanent cures outside of hospital patients in the wards, even in cases of outspoken exophthalmic goiter. I could mention offhand six cases of severe type perfectly well many years afterwards; one of them a case in my own family, well after thirty years, two others of exophthalmic goiter in men and another a woman who is still living years later, and entirely free from any evidence of exophthalmic goiter, though she developed severe myocardial insufficiency, with œdema, during the disease. I have seen other similar cases in my own experience and have also seen in the last few years a great many unsuccessful thyroidectomies. There is no question in my mind at the present moment that just as in the decision between the medical and surgical treatment of gastric ulcer, the problem is very largely a social and economic one. The measures which are necessary for recovery from exophthalmic goiter under medical



rest treatment, are measures which are practically inapplicable to the bulk of patients in a hospital. My father always said that a hospital was the worst place to get results in a patient with exophthalmic goiter. Consequently, for ward patients, one resorts to surgery early. There is no question that without surgery we should be quite hopeless about many of these hospital patients, and yet I cannot feel that the surgery of exophthalmic goiter has solved the problem of the actual pathogenesis of the disease. The fact that von Haberer was able to take out tissue without a trace of thymus in it, fails to convince me that the thymus of that man had anything to do with the improvement. You may remember Dr. John Rogers' enthusiasm over the first results with his serum. He tried it on his own wife, who had one of the worst cases I had ever seen. To his discovery of the serum, she apparently owed her immediate and wonderful restoration to health. The second case did well, the third case not so well. We have seen a number of cases under serum treatment since then, but very few in whom the results have been more than partially satisfactory and failure has been the rule. The majority of us have rather given up any attempt to accomplish results with the serum, although I have seen an occasional case since where, apparently, benefit has come from its use.

We stand to-day face to face with an unsolved problem. The worst of it is there are so many opinions unsupported by adequate evidence, and so much published by people whose actual facts you have to question. We are exceedingly fortunate here in having a chance to watch cases treated by the best surgical methods and followed over a long period of time, as Dr. Halsted does, which is the only possible way we shall ever arrive at a just appraisal of the results. In the course of a few more years we ought to know whether radiation of the thymus gland is going to be valuable or not. At the present moment, I feel that a polite scepticism is the attitude to be taken.

DR. FINNEY: From the surgical standpoint, I should like to add one word. I have been unfortunate enough, as have most surgeons, to lose two or three cases following operation upon the thyroid. In one or two of these cases, the operation was a simple ligation and was followed by death in from 48-60 hours. All the cases, with one exception, that I have seen die from operations upon the thyroid, have died in practically the same way, not immediately, but after two or three days. It seemed to me that some process, just what I do not know, had been started at the time of operation which simply kept on in spite of everything that was done, until the patient died with symptoms very strongly suggesting an intense intoxication of some sort. It appeared then, reasoning purely empirically, that if these patients died from the least thing surgically that one could do, they could not do more than die if the most that one could do was done. I was tempted to put this idea into practice in apparently one of the most hopeless cases that I had operated upon up to that time. I felt that if I did simply so much as a ligation of a vessel and stopped there, the patient would surely die in the manner just described. I had tried, as Dr. Barker suggests, to build the patient up under the rest treatment but there had been no permanent benefit, as unfortunately is sometimes the case. We then resorted to surgery. I removed almost the entire thyroid with the exception of a small piece no larger than the tip of my finger. The patient did just what one would reasonably expect. She was extremely ill for the first 24-48 hours, when a most remarkable change took place and the pulse rapidly came down to normal and remained there. The patient was operated upon two years ago. I heard from her only a short time ago and she had had no recurrence of her symptoms. Since then I have operated upon a group of about 20 cases, among them some of the most unfavorable cases I have had to deal with. I have no definite explanation to offer other than that it is reasonable to suppose, and indeed generally accepted, that in some way or other the thyroid is concerned with the group of symptoms presented by these patients.

Probably the internal secretion of the thyroid and parathyroid is coupled with that of the thymus and the adrenals and perhaps others of the ductless glands and a vicious circle of some sort formed. It would seem that if that vicious circle could be broken beyond repair, the situation could be controlled. If so much thyroid is taken out that there can be no comeback, I thought that perhaps this could be accomplished. That was the idea of the operation. So far, I have had no fatal results. All the patients have followed practically the same course. The charts of these cases are most striking looking. Immediately after the operation, the pulse rises to 160-180. Indeed, sometimes it cannot be counted with certainty. The first 24 hours are an anxious time. If the patient lives through this period, I am confident she will do just what the others have done, *i. e.*, make a good recovery. Here again I feel according to my experience that the old treatment of these thyroid cases is not correct. Most authors advise against the use of morphia and digitalis. It seems to me, however, that these two drugs are especially indicated. I have been in the habit of giving them morphia enough to keep them quiet, and also enough digitalis to steady the heart's action. We have gone on that principle and, so far, the patients thus treated have all done well. Of course, I am constantly expecting to have one who will not do well. It is perhaps expecting too much to think that they will all do well.

In regard to this method of treatment of Graves' disease, I am not making any extravagant claims, I am simply stating my experience up to date. The list of cases operated upon in this way, and the results, seem to me sufficiently long now to justify the further use of the method and also would seem to uphold, perhaps a little more strongly than heretofore, the position occupied by most surgeons.

DR. HALSTED: I should be sorry to emphasize the issue which seems to have arisen between the surgeons and physicians. Dr. Finney and I evidently are in agreement that the medical men should be given a chance, but not too much of a chance, in the treatment of cases of Graves' disease.

It is quite true, as Dr. Janeway says, that many patients are not cured by operation. In our experience this has very largely been due to the fact that not enough thyroid has been removed. The usual operation, the world over, is lobectomy on one side only. When a lobectomy on both sides has been done the patient has with very few exceptions been satisfactorily cured. As to the absolute cures, the percentage in our experience is much smaller than is universally claimed. Usually some traces of the disease remain. We have carefully restudied our cases during the past three years, and conclude that in not more than 25 per cent of the one-sided lobectomies were there no symptoms, discoverable by an expert, remaining. But certainly in 50 or 60 per cent the patients are satisfied with the results.

I should be interested to know if Dr. Finney has observed symptoms of hypoparathyroidism in any of his cases of complete excision of the thyroid gland.

DR. FINNEY: None at all.

DR. HALSTEAD: Dr. Janeway recalls six or more cases which have been permanently cured by medical treatment. The surgeon can quote larger figures. There are many surgeons who credit themselves with more than a hundred cures, and two or perhaps three with a thousand.

With reference to feeding of the thymus, Mikulicz, I think, was the first to suggest it. Many years ago we practiced it in some cases but without significant result. The improvement which has occasionally been reported from feeding of the thymus gland may be analogous to that observed from thyroid feeding in the early thyroid hyperplasias, in the so-called parenchymatous goiter. In cases of this kind the glandular swelling may be reduced while the patient's symptoms are aggravated from the administration of the thyroid extract.



DR. BARKER: There ought to be no conflict between the physicians and the surgeons in the treatment of exophthalmic goiter, and, of course, there is not in this hospital. What we need is the best kind of team-work between physicians and surgeons. A physician will do well to try the effect of judiciously selected medical measures first, but it is wrong to keep an outspoken case of Graves' disease long from the surgeon if the patient does not respond favorably to treatment. It is not right to let the patient go on for a long period with severe thyroid intoxication, until the heart muscle becomes greatly injured, and the surgeon has no chance. This discussion has, I think, emphasized the necessity of a combination of the best work of physicians with the best work of surgeons adequately to care for these patients.

DR. THAYER: I should like to add one word to what Dr. Barker has said. One's position with regard to these cases is not unlike the position of the practitioner with relation to certain instances of appendicitis, particularly some years ago. I think most medical men who practice in a community where they have surgical friends in whom they have confidence, feel it their duty in case of doubt to have a surgeon see the case of appendicitis immediately. I feel in the same way with regard to these instances of thyroid disease. I rarely see a well-marked instance of hyperthyroidism without talking it over with a surgeon at the outset. Such cases should early be observed by both physician and surgeon. I never tire of telling of a case I followed here many years ago—a nurse. I saw her early one morning and advised waiting a little while. Soon I felt that operation was urgent. By 9 o'clock Dr. X. saw her and advised waiting. When he was ready to operate, Dr. Y. saw her and advised a further stay. When he was about to operate, Dr. Z. in turn advised that we wait a little longer. When, finally, the operation was performed, it was almost too late. It has always seemed to me very silly on the part of the physician to constitute himself the supreme judge to decide when a case of hyperthyroidism should be turned over to the surgeon. I know of few conditions where it is more important that the physician and surgeon should proceed hand in hand, as Dr. Barker has said, from the outset. The conscientious practitioner, whether physician or surgeon, is apt to lean toward conservatism. The wise surgeon is not inclined to act immediately in a situation where there has been room for doubt as to the proper method of procedure; and the physician should not expect the surgeon to accept his conclusion without proper deliberation. It is sometimes much to the advantage of the patient if that deliberation is shared by both surgeon and physician from the outset.

DECEMBER 21, 1914.

**Paroxysmal Hæmoglobinuria. Exhibition of Case. DR. G. A. BATTEN.**

Male patient aged three and a half years. Father and mother and two older children living and well. No history of lues in family. Nothing in past history bearing on present illness, there being especially no history of early luetic manifestations. The present illness began with sudden onset on November 1 of this year. Patient had a chill, fever and afterwards was said to have voided bloody urine for a period of about one week. After this he was apparently well, except that he was slightly pale, until December 12, when he had another chill and again voided bloody urine. He was brought to the hospital on December 15, three days after the onset of the last attack.

On examination: very pale, enlarged liver and spleen; general glandular enlargement, also slight jaundice. The blood showed w. b. c. 29,000, r. b. c. 1,800,000, hæmoglobin 37 per cent. On examination the urine was found to be black in color, and gave a distinct guaiac test. Microscopic examination showed a few white blood cells, a few granular casts, but no red blood cells. The patient was put to bed. A specimen of urine examined 24 hours later was

practically normal, was light amber in color and there was no hæmoglobin present. Because of the history and because he had a hæmoglobinuria which cleared up 24 hours after being put to bed, we thought we had to deal with a case of paroxysmal hæmoglobinuria. As further evidence that this was a case of true paroxysmal hæmoglobinuria, we did a test first described by Donah and Landsteiner and subsequently confirmed by Dr. Moss, working in this hospital, and many others. These observers found that hæmolysis of the blood of hæmoglobinuric patients took place if the temperature was first lowered and then raised. To do this test we placed 0.25 cc. of the patient's serum in each of two test tubes and to each we added 0.25 cc. of a 5 per cent suspension of the patient's corpuscles. We reduced the temperature of one to 0° and then raised it to 37°, when complete hæmolysis promptly took place. The other tube was kept at 37° without first lowering to 0°, and no hæmolysis resulted.

In this case it seemed reasonable to us to explain the general glandular enlargement and the enlarged liver and spleen on the basis of hereditary syphilis, and the anæmia as a result of this infection, plus the severe hæmoglobinuria. The relationship of syphilis and paroxysmal hæmoglobinuria seems to be a close one. An analysis was made by Cook in the *American Journal of the Medical Sciences*, 1912, of all the cases reported prior to that time. He found that 90 per cent of the cases gave a positive Wassermann. Whether or not a positive Wassermann in this disease is due to a luetic infection, or whether it may be due to some other condition, I do not wish to discuss now. In this case it seems justifiable to make a diagnosis of hereditary syphilis because of the clinical findings, and also because of the fact that both the blood of the patient and that of his mother gave a positive Wassermann.

DISCUSSION.

DR. THAYER: I should like to know if there was any hæmoglobinuria while in the hospital?

DR. BATTEN: None after the first day of hospital care.

DR. THAYER: We had several years ago a very remarkable instance of hæmoglobinuria in a woman with a very striking anæmia which bore some resemblance to pernicious anæmia. The hæmoglobinuria showed a remarkable periodicity, appearing regularly over considerable periods of time in the early morning hours, say from 4-6 o'clock. We tried in many ways to see if we could not produce this same condition at some other hour, but unsuccessfully. The patient came to the hospital for this condition on two successive years, each time having a moderately enlarged spleen. The Wassermann reaction was negative. In view of the interesting results following splenectomy, the possibility of performing the operation for her anæmia entered our minds. Was there any periodicity in the case exhibited to-night?

DR. BATTEN: No, there was none whatever.

\* **Gaucher's Disease, with Report of Two Cases in Infancy.** DR. J. H. M. KNOX, JR., and DR. W. H. WAHL, Cleveland, Ohio.

The cases which form the basis of this report are those of two infants, one of whom is at present in the Harriet Lane Home of this hospital.

The first patient, a girl 9 months old, was brought to the Thomas Wilson Sanitarium in June, 1912, with a history of never having gained. There was no history of acute onset, nor of very marked digestive disturbances. She had begun cutting her teeth at about 7 months; had never walked and could not hold her head up. The family history was of importance. The patient was Jewish, the youngest of 11 children, 3 of whom had died in infancy,

\* This report will appear in full in a subsequent issue of THE JOHNS HOPKINS HOSPITAL BULLETIN.



and one at the age of 14 with what was said to be tuberculosis of the hip. Six children were living and well. The history at the sanitarium was uneventful. There were almost no symptoms of acute intestinal derangement; there was some indigestion and now and then distension, which was relieved for a time, only to reappear later. The patient lost progressively in weight and died, at the age of 11 months, of exhaustion. Repeated von Pirquet tests were negative. The Wassermann was negative. Physical examination on admission showed a pale child, with slight bronzing of the skin, more pronounced over the face. No jaundice. Enlargement of abdomen due to tremendous hypertrophy of both liver and spleen, the latter extending considerably below the umbilicus, firm and hard to the touch but rather smooth. The liver extended to about the same level, the left lobe extending 1 or 2 inches below the costal margin. On palpation it was firm and gave an impression of tenseness and a certain degree of resiliency. There was only a slight general glandular enlargement. The blood-picture was almost normal. The leucocytes ranged from 10,000-22,000 on several counts. Two or three days before death they rose to 35,000. The differential count showed about an equal proportion of mononuclear and polynuclear cells, until shortly before death when, with the increase in the leucocytes, there was a marked increase in the mononuclear element. No diagnosis was made. We discussed Banti's disease, although this is of extremely rare occurrence at this age. The last blood count led us to think that we had perhaps missed a case of lymphatic leukemia. The autopsy was done by Dr. Wahl.

Some 16 months later, the same mother brought to the dispensary at the Harriet Lane Home, a second child, almost the counterpart of the one seen at the Thomas Wilson Sanitarium, an infant of 4 months, with no history of acute onset, breast fed exclusively, but one who had never thrived. The patient presented an enormously enlarged liver and spleen, together with slight general glandular enlargement. It weighed only 8 lbs. She was treated in the dispensary for several months and was afterwards admitted to the house, where she still remains. She has had slight leucocytosis, ranging from 11,000 to 26,000. At Dr. Howland's suggestion, treatment with radium was begun in October. The leucocytes fell in a few days from 20,000 to about 6400 and have remained extremely low since, the last count being about 2200.

The findings at autopsy on the first case and the examination microscopically of a gland removed from the second child, showed the same characteristic cellular changes which were first described by Gaucher in 1882. Since then 18 cases have been definitely proven at autopsy or by examination of the spleen following operation to belong to this group. It is interesting that only two of these patients have been males. The age seems to be unimportant, because of the long duration of the disease. If our two patients belong to this group, they are apparently the youngest whose cases have been reported. The oldest patient, above 18, was 44 years old.

Dr. Knox then referred to the most characteristic symptoms and physical signs of the condition, which apparently does not descend from one generation to another, but frequently appears in several children of the same generation. As to results, one can only say that the disease is a long and tedious one. Splenectomy was done in 9 cases and there were 3 deaths immediately following the operation. In the 6 other reported cases, the patients were living. The chief relief from operation has been in the removal of the large abdominal mass. The disease itself has not been checked.

Dr. Knox was followed by Dr. Wahl, who first described the anatomical findings of the organs and glands, taken from Case I, macroscopically and then exhibited various microscopical sections of the same. In all the organs the same condition was marked, clusters of large, pale cells, somewhat resembling fat cells, being predominant. As to the exact nature of these cells, Dr. Wahl declined as yet to give any definite opinion, but he called particular attention to the marked infiltration by them of each organ and to the apparent activity of their growth.

## DISCUSSION.

DR. HOWLAND: To the conditions which have generally been recognized as causing enlargement of the spleen in infancy must be added another. This, up to the present time, has not been appreciated. It is one that would hardly be thought of, for manifestations of Gaucher's disease in infants, if these cases are to be considered Gaucher's disease, are quite different from those in older children or adults. The course of the disease is much more rapid, the lesions more widely spread and the splenic enlargement relatively not so great. Years ago, as a hospital interne, I saw the patients reported by Bovaird. They were older children, the disease had been recognized for several years and in each case the spleen filled two-thirds of the abdomen. The microscopic changes in the spleen and other organs have been described as specific, and if this is so it would seem that these two cases described by Dr. Knox should be classed under Gaucher's disease, even though clinically they are so different from the reported cases.

DR. JANEWAY: I have been much interested in this presentation as I had the opportunity of seeing a few of the previously reported cases, among others the family group presented by Brill, Mandelbaum and Libman. It may interest the society to know just how these cases came to be so beautifully studied. There were four members of the family with enlarged spleens. The first case came to autopsy as the result of a pericarditis and the diagnosis was made in this way. The second case happened to meet with a bicycle accident within one block of Mt. Sinai Hospital in New York and was brought in and came to autopsy. But for that, it would probably never have been added to the list.

I saw the case of Downes before operation. It brought up certain problems of diagnosis and added very considerably in my mind to the difficulty in distinguishing these splenomegalies. The patient was a young woman from the South, with no family history of enlarged spleens. She had had rather marked anæmic attacks, dating back to early life. Some of these had been of considerable severity, so that she was incapacitated. She was a musician and for months at a time would have to give up practicing on account of her extreme weakness. When I saw her, she had been observed in the New York hospital for some weeks. She was suffering from severe secondary anæmia, with extreme leukopenia the white cells always being below 2000 and frequently below 1000. She had a large spleen, liver just palpable and nothing else. The picture, with the excessive leukopenia, was so suggestive of splenic anæmia, or the early stage of Banti's disease, that I gave that as my opinion. The operation was a successful splenectomy. The sections were carefully examined and there was no question as to the diagnosis of endothelial hyperplasia.

It seems to me, therefore, that the clinical picture of Gaucher's disease is to be considered as one which scarcely permits of positive diagnosis. With a familial history, the diagnosis may be made with certainty, but in the absence of such history it may be impossible to separate it from the so-called splenic anæmia.

DR. THAYER: I asked Dr. Knox a few moments ago if he were familiar with the case of Stengel, which was reported some years ago before the Association of American Physicians. He tells me that Brill has ruled it out. Stengel's microscopic specimens bore a striking resemblance to those shown here to-night. His case was one regarded as Banti's disease until operation. On examination of the spleen after splenectomy, the striking feature was that the endothelial masses stood out so plainly, just like definite tumors. Indeed they could be seen on the surface of the spleen. It was remarkable that it had not been felt as a nodular spleen *intra vitam*. The structure of these areas was very similar to that shown in the sections by Dr. Wahl to-night. Of course I speak from memory, but should be glad to know why Brill ruled that case out. I remember that there was a great deal of discussion at the time, and I believe Dr. Welch acquiesced in the view that the case was an instance of Gaucher's disease.



DR. WAHL: I think I can answer your question. Dr. Karsner of Cleveland was the man who did the autopsy on Stengel's case. Later on they found tuberculosis. Dr. Karsner thought the case might have been one of Gaucher's disease, but on account of the presence of the tubercle bacillus and of definite tubercles the other men were doubtful and so the case was ruled out.

#### Medical Experience in Siam. DR. E. C. CORT.

After a brief outline of the topography of the country and the ethnology and religion of the people, Dr. Cort discussed the principal diseases found in Siam. The sanitary conditions of the country are practically nil and the people know nothing of the cause of disease or of its prevention.

Small-pox is extremely common and no precautions are taken by the natives against the disease. Vaccination has been introduced, however, where Western civilization has penetrated.

Malaria prevails generally, 90 per cent of the people examined by Dr. Cort showing signs of chronic malaria. Although the disease is practically endemic, severe epidemics are not infrequent with large numbers of cases of the cerebral type, the attacks coming on as quickly as apoplexy. In these instances, a patient who had perhaps been having fever, would suddenly fall absolutely unconscious and remain in coma until death. The parasite was usually the æstivo-autumnal, of a very malignant form.

Infection with the hookworm is very common, some statistics indicating that at least 90 per cent of the people harbor the parasite.

Tuberculosis also is extremely common. The natives, of course, have no ideas with regard to the care and treatment of the patients. The only thing that saves a great many is the fact that the native architecture is of such a type as to prevent them from closing their houses tightly, and in this way they get a certain amount of fresh air and sunlight.

Another disease frequently encountered is dysentery, very largely of the amœbic type. The use of emetin in the treatment of this disease has been most interesting. One male patient with acute dysentery was having 60 stools a day, practically pure mucus and blood. He was extremely anæmic and very weak. He was put on emetin, one-half grain every four hours, with a little morphia and strychnine. Although he came into the hospital on a stretcher, he went home at the end of five days, carrying his own baggage, say-

ing he felt too well to stay any longer. At the end of seven or eight weeks, his daughter reported that he was still in very good health. The result was very remarkable, as he must have had severe ulceration. Dr. Cort mentioned other striking results obtained from the use of emetin, among them a case of amœbic abscess and one of enlarged liver.

An interesting condition to be investigated is that of beri-beri, which is popularly supposed to be due to eating over-milled rice. A severe epidemic of both the wet and dry forms (fatal to 50 per cent of the patients involved), which followed a flood some years ago, would seem to indicate that perhaps other factors than the eating of over-milled rice are involved in the causation of this disease.

Leishmania infections form another group of cases to be cleared up. Dr. Cort had had five such cases, all the patients coming from the same mountain district. In one the spleen actually extended into the pelvis.

Venereal disease, which is almost unknown in the country districts, is quite common in the cities, particularly the seacoast towns. Over 90 per cent of the officers and men in the army, and also government employees, are infected with one or both diseases. The marriage and divorce customs are extremely lax, and this factor greatly aids the spread of the infection.

The most common surgical infection is calculus, the patients ranging from six months in age to 83 years. With one or two exceptions, every case of calculus in men over 30 seen by Dr. Cort, was accompanied by arteriosclerosis. The latter condition is extremely prevalent in men of 40 and older.

Leprosy is of frequent occurrence, the afflicted persons congregating in leper villages after having been driven from their homes.

Eye cases are also very numerous.

With less than ten doctors for many millions of people, Dr. Cort spoke of the hope of establishing a medical school in Siam, which would provide for the training of competent natives to help cover this enormous field.

#### THE JOHNS HOPKINS HOSPITAL HISTORICAL CLUB.

DECEMBER 14, 1914.

Superstition and the Doctor. MR. OWEN WISTER.

## TITLES OF PAPERS APPEARING DURING THE YEAR, ELSEWHERE THAN IN THE BULLETIN, BY PRESENT AND FORMER MEMBERS OF THE HOSPITAL OR MEDICAL SCHOOL STAFF.

#### ABEL, J. J., ROWNTREE, L. G., and TURNER, B. B.

On the removal of diffusible substances from the circulating blood of living animals by dialysis.—*J. Pharmacol. & Exper. Therap.*, 1914, v, 275.

On the removal of diffusible substances from the circulating blood of living animals by dialysis. II. Some constituents of the blood.—*J. Pharmacol. & Exper. Therap.*, 1914, v, 611.

Plasma removal with return of corpuscles (Plasmapheresis).—*J. Pharmacol. & Exper. Therap.*, 1913-14, v, 625.

#### ABEL, J. J., and TURNER, B. B.

On the influence of the lymph hearts upon the action of convulsant drugs in cardiectomized frogs.—*J. Pharmacol. & Exper. Therap.*, 1914, vi, 91.

#### AUER, J.

The effect of intraspinal injections of serums with and without preservatives.—*J. Am. M. Ass.*, 1914, lxii, 1799.

The functional analysis of anaphylaxis.—*Forchheimer's Therapeutics Int. Dis.* [Billings & Iron.] N. Y. & Lond., 1914, v, 39.

#### AUER, J., and MELTZER, S. J.

The fatal action of magnesium salts by absorption from the intestines and the resuscitation by calcium.—*Proc. Soc. Exper. Biol. & M.*, 1914, xi, 95.

#### BAER, W. S.

Traitement de l'ankylose.—*Rev. d'Orthop.*, 1914, 3<sup>me</sup> s. v, 259.

#### BAETJER, F. H., and FRIEDENWALD, J.

On the diagnosis of incomplete forms of pyloric stenosis by means of the X-ray.—*Boston M. & S. J.*, 1914, clxxi, 261.

#### BAETJER, F. H., and HAMMAN, L.

Pulmonary physical signs and Roentgen-ray findings in healthy adults.—*Arch. Int. Med.*, 1914, xiv, 757.

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#### BARKER, L. F.

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Some elements of danger in eugenics.—*Baltimore Evening Sun*, 1914, January 26.

Physicians, the people, and the press.—*Bull. Med. & Chir. Fac. Maryland*, 1913-14, vi, 155.

The diet in typhoid fever.—*J. Am. M. Ass.*, 1914, lxiii, 929.

Some of the commoner types of diseases of the endocrine glands.—*J. Med. Soc. N. Jersey*, 1914, xi, 493.

The diagnosis and treatment of the commoner thyreopathies.—*South. M. J.*, 1914, vii, 1.

#### BEALL, F. C.

Cancer of the breast.—*Texas State J. M.*, 1913-14, ix, 369.

#### BEALL, K. H.

Pellagra.—In *Mod. Med.* 2 ed. (Osler & McCrae), Phila. & N. Y., 1914, ii, 472.



- BERNHEIM, B. M., and JONES, A. P.  
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- BERNHEIM, B. M., WHIPPLE, G. H., and STONE, H. B.  
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- BERNHEIM, B. M., and WROTH, P.  
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## NOTES ON NEW BOOKS.

*Sclero-Corneal Trephining in the Operative Treatment of Glaucoma.* By ROBERT HENRY ELLIOTT, M. D. Second edition. \$3 net. (New York: Paul B. Hoeber, 1914.)

It is interesting to note that this work has passed into its second edition before the end of its first year of life. That the question of sclero-corneal trephining for glaucoma has appealed to the common sense of ophthalmologists all over the world is evident from the widespread interest Col. Elliott's work has aroused, and few will be found without the first edition. The book has been so generally reviewed and its points subjected to such sifting in medical discussions within the past year that little remains to be said of this new edition. The chapter dealing with sclero-corneal trephining (Chapter V) has been greatly expanded. Chapter XI has been completely revised and here one will find the results of four years of trephining in Madras. Chapter XII is new and puts forward the experience and statistics of a number of ophthalmologists.

Those who have tried this operation are pretty well agreed that it is especially valuable in chronic simple glaucoma. It seems equally clear that it has not converted nor probably ever will convert many to the view of its superiority over iridectomy in acute inflammatory glaucoma. In chronic non-inflammatory glaucoma it is perhaps a better procedure than iridectomy, but even here, by treading on better known ground and doing the iridectomy, one might after all, certainly in many cases, be subserving the best interests of the patient. One should bear in mind that iridectomy, even in chronic simple glaucoma, has saved its thousands and while there remains much to be desired on this point we are hardly called upon as yet to abandon the procedure entirely. It seems that the performance of an iridectomy along with the trephining has a very important influence for good upon the outcome of this operation and that we cannot afford to omit this step. When we come to the question of the remote or ultimate results of the operation we confess to a feeling of some little pessimism and we are convinced that the last word upon this question cannot be spoken for several years. It is hard to believe that an eye with an opening into its interior covered by a prominent bleb, with constant friction going on between the surface of the bleb and the upper lid and with bacteria everywhere on the surface of the conjunctiva, can escape infection for very long. We are still in the dark as to the true nature of glaucoma and from recent reports it would seem that late infection might after all prove the ultimate undoing of many of these cases.

*A Manual of Practical Hygiene.* By CHARLES HARRINGTON, M. D., Fifth edition. Revised and enlarged by MARK WYMAN RICHARDSON, M. D. (Philadelphia: Lea & Febiger, 1914.)

This well-known work was first revised several years ago by Dr. Richardson, who edited the third edition shortly after Dr. Harrington's death. Since then a fourth and now a fifth edition has appeared. This last edition has had the benefit also of the collaboration of the officials of the State Board of Health of Massachusetts of which Dr. Richardson is secretary. The original form of the book is preserved, and the treatment of the various branches of the science remains as exhaustive as it was formerly. On the chemical aspects of hygiene the book is especially strong, and the chapter on foods, comprising 289 pages and divided into eight sections, is one of the most comprehensive presentations of this subject in English. The chapter dealing with hygiene of occupations, prepared by Dr. William A. Hanson, is especially attractive and is illustrated by a number of instructive photographs. Military hygiene is also ably presented in a section of 60 pages, and naval and marine hygiene somewhat more briefly. Medical inspection of schools is considered by Mr. George H. Martin, formerly secretary of the State Board of Education, and is an excellent résumé of the duties of medical school inspectors.

Considering the great importance of school hygiene, however, the treatment of this subject seems inadequate. We look in vain for some detailed discussion of the important questions which arise in regard to school children. How many hours of work, for instance, should be required of children of various ages? What should be the hours of school attendance and how should they be distributed? At what age should children begin school? Should attendance at kindergartens be encouraged? These and many other questions are vital and need an answer from the medical and from the educational point of view. A still more important question possibly relates to the intimate relationship between the incidence of infectious diseases in a community, and the age at which school attendance is compulsory, a topic emphasized so much by the English sanitarians. A book which is so distinctly the standard reference book on hygiene in America should, we feel, give more complete and thorough discussion of such questions, although this criticism is equally applicable to the other text-books on hygiene published in this country. All in all, Richardson's edition of Harrington, we predict, will remain for a long time our best authority in this field.

W. W. F.



# BULLETIN

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## THE OSTEOGENIC POWER OF PERIOSTEUM: WITH A NOTE ON BONE TRANSPLANTATION. AN EXPERIMENTAL STUDY.

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AND

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### INTRODUCTION.

The appearance of Macewen's monograph<sup>1</sup> caused considerable discussion among those interested in the growth of bone. His experiments seemed to show that periosteum was not a bone-producing tissue, but that its function was simply that of a limiting membrane. This, of course, was not in accordance with the principles accepted for many years, and it was difficult to adjust ourselves to his ideas without first-hand experimental proof.

The literature on this subject has been fully commented on in a number of recent experimental and clinical papers, so we shall not consider it at this time. Suffice it to say that some investigators found osteogenic power in periosteum and others did not.<sup>2</sup>

<sup>1</sup> "The Growth of Bone." William Macewen, F. R. S. (1912).

<sup>2</sup> In many of the original reports there is paucity of detail as to whether macroscopic particles of bone were adherent to and transplanted with the periosteum. We feel that definite conclusions as to the bone producing power of periosteum can only be drawn from

We approached the subject with, as far as possible, unbiased minds, although, if we had a leaning more one way than another, it was to the opinion that periosteum was a bone-producing tissue. In order to clear the matter up for our own satisfaction, we have repeated during the last two years many of Macewen's experiments, and also have carried out a number of our own.

One hundred and sixty-seven experiments were done on 50 dogs and 17 rabbits. The ordinary run of laboratory animals were used, although as far as possible young animals were selected. Ether anesthesia was used in each experiment.

*Technic.*—The part was shaved or the hair was removed with a solution of sodium sulphide. The skin was washed with

those experiments in which every effort was made to remove the periosteum without particles of the underlying bone. The character of the wound healing is also very lightly touched upon in many of these papers. It is also well to bear in mind that Ollier's classic work on bone and periosteum was done in the pre-antiseptic period of surgery.



green soap and water, then with alcohol, followed by ether. After the skin was thoroughly dry it was painted with tincture of iodine, 2.5 per cent. The iodine solution was also occasionally used in the open wounds and after suture of the skin. Fine black silk was the ligature and suture material used throughout. The wounds were closed in layers wherever possible. Collodion and gauze dressings were applied when necessary. Unless otherwise stated the healing will be understood as *per primam*. Land-mark sutures were used when periosteum or bone was placed in the soft parts. *The results were controlled by careful dissection and by X-ray and microscopic examinations.*<sup>\*</sup>

In these experiments, except where definitely specified to the contrary, care was taken not to remove any particles of bone with the periosteum. This was accomplished by outlining the periosteal flap down to the bone with a scalpel, and starting it away from the bone with a blunt instrument. Then by means of a small, very firm gauze pad, grasped in an artery clamp, the periosteum was removed without disturbance of the surface of the bone.

Microscopic examination shows that the periosteum with the greater part of the underlying osteoblasts may be removed in this way.

For convenience in comparing the results we have divided the experiments into groups.

#### GROUP I.

##### THE TRANSPLANTATION OF FREE FLAPS OF PERIOSTEUM.

*A. The Transplantation of Free Periosteum Without Bone Particles Into the Muscle or Subcutaneous Tissue of the Same Animal.*

**TYPICAL EXPERIMENT.**—Mongrel dog; about 6 months old. *Operation:* The right femur was exposed and the periosteum was removed from 5 cm. of its circumference. The periosteum was then placed in the body of an adjacent muscle, and stretched between two sutures. The wound was closed. After 30 days the site of the transplant was occupied by a thin band of fibrous tissue, in which no bone could be made out. There was no thickening of the area from which the periosteum had been removed. The nourishment of the bone was unimpaired.

**SUMMARY.**—We made 21 experiments; 16 on dogs and 5 on young rabbits. The flaps of periosteum varied in size from that of the entire femur to an area 1 cm. wide from the circumference of the radius. In one experiment the periosteum from a section of fibula 1.6 cm. long was turned inside out in stripping it from the bone, thus exposing the surface next to the bone. In six experiments the periosteum was placed in the subcutaneous tissue, and in 15 in the muscle tissue. The periosteum was spread out and sutured in position in 7 experiments, and in 14 it was bunched. The specimens were examined 8, 14, 15, 19, 30, 31, 35, 78, 94, 95, 104, 113 and 133

<sup>\*</sup> We take this opportunity of expressing our thanks to Dr. Harry F. Baetjer for the X-ray plates; and to Mr. C. R. Thomas for his aid in the operative experiments.

days after operation, and in no instance could any growth of bone be detected.

*B. The Transplantation of Free Periosteum Without Bone Particles Into the Muscle or Subcutaneous Tissue of Another Animal of the Same Species.*

**TYPICAL EXPERIMENT.**—Fox terrier; about 4 months old. *Operation:* The periosteum obtained from a section of the radius, 3 cm. long, was bunched and placed in the subcutaneous tissue. The wound was closed. After 123 days no new bone formation was found. The site of the transplant was easily recognized by means of the land-mark sutures, but the transplant itself had entirely disappeared.

**SUMMARY.**—Five experiments were done on dogs. The periosteum was obtained from the circumference of a resected portion of the radius, varying in length between 2.2 and 3 cm. The transplants were placed in the subcutaneous tissue in 3 experiments and in the muscle in 2. In each experiment the periosteum was bunched. The specimens were examined 27, 91, 121, 123 and 126 days after operation, and in no instance was any growth of bone detected.

*C. The Injection Into the Soft Parts of Small Bits of Periosteum, Without Bone Particles, in Suspension.*

**TYPICAL EXPERIMENT.**—Young rabbit. *Operation:* The tibia was exposed and a flap of periosteum 2.7 x .5 cm. was removed and cut into very small pieces. This was shaken up in 15 minims of Ringer's solution. This mixture was injected by means of a syringe through a stab wound, into the subcutaneous tissue of the thigh, at some distance from the opening. The wound was closed. After 29 days no new bone could be demonstrated, and no sign of the periosteum could be found.

**SUMMARY.**—Six experiments were done on rabbits. The periosteum was obtained from the tibia in each instance. The flaps varied between 2 and 3 cm. in length by .5 cm. in width. The periosteum was cut into small bits with scissors, and was shaken up with from 10 to 15 minims of normal salt solution in 3 experiments, in Ringer's solution in 2 experiments, and in blood in 1 experiment. The injections were made into the subcutaneous tissue and muscle, three times each. The specimens were examined 10, 13, 29, and 32 days after injection. In 1 experiment, 32 days after the injection of periosteum in salt solution, a single oblong bit of calcified tissue, 4 x 2.5 mm., was found. There is doubt, however, as to the origin of the fragment, as the injection was made subcutaneously into the lateral aspect of the middle of the thigh, while the calcified tissue was found close to the joint beneath the rectus muscle. Microscopic examination showed deeply staining calcified material with no bone. In the other experiments no bone formation could be demonstrated.

These three groups of experiments show that neither free auto- nor iso-periosteum has the power of bone production when transplanted into soft parts, even though a considerable number of osteoblasts be adherent to the transplant.

*D. The Transplantation of Free Periosteum With Thin Bone Shavings Attached, Into Soft Parts of the Same Animal.*



**TYPICAL EXPERIMENT.**—Mongrel dog; about 1 year old. *Operation:* A flap of periosteum, 3 cm. in length by one-half the circumference of the femur in width, was removed, with thin shavings of bone attached to it, and was placed in a pocket burrowed in muscle tissue. After 128 days a small area of bone was found, which cast a shadow on the X-ray plate. Microscopically new bone was demonstrated.

**SUMMARY.**—Seven experiments were done on dogs. The periosteal flap with shavings of bone attached was obtained from the femur in each instance. It was either raised with a very thin chisel, or roughly with a curette. The flaps varied between 3 and 3.5 cm. in length by 1 cm. to one-half the circumference of the femur in width. Such a flap was placed in the subcutaneous tissue six times and in muscle tissue once. The specimens were examined 11, 64, 67, 127 and 128 days after operation. In each experiment there was definite bone formation. This bone growth was very much smaller than might have been expected from the size of the transplant with attached shavings. In no experiment was the new bone more than 4 mm. long by 1 mm. thick. In no instance was there more than a very slight roughening of the surface of the femur, from which the periosteum and bone shavings had been removed.

This group of experiments shows definitely that free periosteal flaps with bone shavings attached produce new bone. When compared with the results of transplantation of free periosteum without bone particles it shows that bone particles and accompanying osteoblasts are necessary for the production of bone. It may be that this new bone would eventually have been absorbed, as the specimens contained a great deal less bone than was originally transplanted, in spite of the fact that so large a surface was exposed for the reception of a new blood supply.

*E. The Transplantation of Free Periosteum Without Bone Particles, Congealed in a Blood Clot, Into the Subcutaneous Tissues of the Same Animal.*

**TYPICAL EXPERIMENT.**—Fox terrier; about 8 months old. *Operation:* A flap of periosteum, 3.5 x .75 cm., was removed from the shaft of the femur. It was bunched and congealed in a blood clot, which was then placed in a pocket burrowed in the subcutaneous tissue of the thigh. The pocket was closed with a purse-string suture. After 20 days, at the site of the transplant there was a small amount of clear fluid, but no sign of the periosteum.

**SUMMARY.**—Eight experiments were done on dogs. The periosteum was obtained from the shaft of the femur. The flaps varied between 2 and 4 cm. in length, by .75 cm. to one-half the circumference of the femur in width. In each experiment the periosteum was bunched and congealed in a blood clot, which was placed in the subcutaneous tissue. The specimens were examined 20, 87, 100, 112 and 113 days after operation. In 4 experiments, after 20, 87, 100 and 113 days, a well-marked scar was found, but no evidence of bone formation. In 4 others (100 and 112 days) a tiny calcified mass, scarcely 1 mm. in diameter, was found at the site of the trans-

plant. In the 100 days' specimen there had been a slight superficial infection of the skin wound, and although this was at some distance from the transplant, it may have had an influence on the deposit of lime salts. Microscopic examination showed definite new bone formation in both specimens, but it was much more marked in the one than in the other. In the 112 days' experiments, on the other hand, the healing had been *per primam*, and the calcified material was smaller than in the 100 days' experiment. Microscopic examination showed calcified material, but no definite bone tissue.

Calcification occurred in 4 of the 8 experiments. In 1 of these a small amount of bone was demonstrated microscopically. In another only a tiny particle of bone could be found, while in the 2 other experiments showing calcification no bone could be found. It is well known that calcification in blood clots occasionally occurs, and it is possible that the presence of periosteum without bone particles in the blood-clots may have influenced the deposit of lime salts. Taking into consideration the preceding experiments, it is probable that in the 2 experiments in which bone was definitely demonstrated some particles of bone had accidentally been transplanted with the periosteum.

## GROUP II.

### THE TRANSPLANTATION OF PEDUNCULATED FLAPS OF PERIOSTEUM.

*A. The Transplantation of Pedunculated Flaps of Periosteum Without Bone Particles Into or Around Adjacent Muscles.*

**TYPICAL EXPERIMENT.**—Mongrel dog; about 10 months old. *Operation:* The radius was exposed and an area of periosteum, 4 x 1.25 cm., was outlined on three sides. The flap was raised, care being taken not to disturb the bone. The base of the flap was situated at the lower epiphyseal line. The flap was then passed around adjacent muscle tissue, and the free end brought back and sutured to the cut edge of the radial periosteum. The wound was closed. After 151 days no new bone formation could be demonstrated. The periosteal flap had entirely disappeared. There was very slight thickening of the bone over the area from which the periosteum had been raised.

**SUMMARY.**—Four experiments were done on dogs. The radius was utilized in each instance. The flaps were from 1 to 1.5 cm. wide and from 3 to 4.5 cm. long. In 2 experiments the pedicle was left attached to the shaft of the bone, and in 2 to the epiphyseal line. In one of each the flap was drawn out into the adjacent muscle tissue, and in the others the free end was sutured to the cut edge of the radial periosteum. The specimens were examined 151, 212, 216 and 220 days after operation. In no instance could any bone formation be demonstrated. In 2 experiments, the surface from which the periosteum was raised was scarified, and in each of these there was slight roughening of the bone at the point of scarification. This also occurred in 1 experiment in which the bone was not scarified, while in the other the bone was perfectly



smooth. The roughening could be felt rather than seen. It was easy to demonstrate the area from which the flap had been raised, as the line of incision was outlined at the time of operation with sterile India ink, and enough remained to definitely show the location.

These experiments show that there is no bone formation from periosteum, even though the periosteal flap is still attached by a pedicle to the bone itself.

*B. The Transplantation of Pedunculated Flaps of Periosteum, With a Thin Film of Bone Attached, Into Adjacent Soft Parts.*

**TYPICAL EXPERIMENT.**—Mongrel dog; about 6 months old. *Operation:* The femur was exposed and an area of periosteum, 3 x .8 cm., was outlined on three sides and raised with a thin film of bone attached. The adjacent muscle tissue was sutured beneath it, so that the pedunculated periosteum-bone flap was held away from the shaft of the femur. The wound was closed. After 34 days the flap was found thickened throughout. It was firmly attached to the femur by much thickened bone. Cartilage could be seen in the thickened area, and cartilaginous bone was demonstrated by microscopic examination. The X-ray picture showed new growth of bone throughout the flap. The shaft of the femur was thickened at the base of the flap, but there was very little new bone growth over the area from which the flap had been raised.

**SUMMARY.**—Eight experiments were done on dogs; 4 on the ribs and 4 on the femur. The specimens were examined 23, 34, 50 and 171 days after operation. The flaps on the femur varied from 2 to 3 cm. in length, by .8 to 1 cm. in width; on the ribs from 1 to 3 cm. in length, by the width of the rib. On the femur the muscles were sutured beneath the flap, and on the ribs the adjacent soft parts. In 2 experiments the flap was accidentally detached from the rib, but its attachment was placed in contact with the denuded bone and secured. In each experiment the bone-periosteal flap lived and new bone formed from it. The intermediate cartilage stage was noted in the femur flaps, but not in the rib flaps.

These experiments show that pedunculated flaps of periosteum with a thin bone film will live and produce new bone and become greatly thickened. This thickening was considerably reduced in the 171 days' experiment, as might be expected. These experiments are of some clinical interest, as this is undoubtedly what happens when a strip of periosteum with bone, still attached to the bone at one end, is raised by trauma, and accidentally implanted in adjacent soft parts. The contrast, between what happens in this group and in the case of the pedunculated flaps of periosteum in soft parts without bone particles attached, is very significant and further strengthens the conclusion that the presence of bone on periosteum is necessary for the production of bone, (Fig. 1).

**REMARKS.**—From the results obtained in Groups I and II, we find that free periosteum, without bone particles adherent to it, will not produce new bone when transplanted into muscle or subcutaneous tissue of the same animal; that this is also true for iso-transplants of periosteum alone; that new bone

was found in 2 experiments and calcification in 2, in which the free periosteum had been congealed in a blood-clot before transplantation (in the two experiments in which bone was found, it is possible that small bits of bone were accidentally transplanted with the periosteum); that free periosteal flaps with thin bone shavings attached did produce bone in each experiment; that pedunculated flaps of periosteum without bone did not produce bone in a single instance; that pedunculated flaps of periosteum with a thin film of bone did produce bone in every instance.

The clinical use of the free transplantation of periosteum is of value only in those instances in which periosteum has been employed to fill in defects. In such operations the result depends entirely on the formation of bone, and bone will not be formed unless bone is transplanted with the periosteum. The chances are that even the new-formed bone will eventually be absorbed. The pedunculated periosteal flap, with a thin film of bone attached, is of considerable interest, as it may help to explain some of the remarkable post-traumatic X-ray plates which are sometimes difficult to understand.

The nourishment of the bones was in no way affected by stripping off the periosteum, unless the nutrient artery was interfered with. In those instances in which the artery was cut, the bone was apparently normal, but the X-ray showed changes in its nutrition. In very few instances was the bone from which the periosteum was stripped visibly thickened, unless it had been considerably traumatized. In some instances in spite of chiseling and scraping there was practically no overgrowth of new bone.

The defects in the periosteum were, in many instances, replaced by a fibrous membrane, which resembled the periosteum in appearance, but was much more tightly adherent to the bone than was the normal periosteum. In some instances the muscle tissue was tightly adherent to the bone.

### GROUP III.

THE SUBPERIOSTEAL RESECTION OF BONE, THE PERIOSTEAL TUBE, AS FAR AS POSSIBLE, BEING LEFT UNDISTURBED.

**TYPICAL EXPERIMENT.**—Mongrel dog; about 8 months old. *Operation:* A section of rib 3 cm. long was removed subperiosteally and the periosteal tube was closed. There was no blood-clot between the rib stumps. After 100 days the continuity of the rib was found restored, and except for a very slight thickening of the rib ends and the line of sutures in the periosteum, it would have been difficult to locate the site of operation.

**SUMMARY.**—Eleven experiments were done on dogs under 8 months old. In 8 experiments sections of rib were removed and, in 3, sections of the radius. The length of the pieces of rib removed varied between 1.5 and 3 cm. The length of the sections of radius varied between that of the entire radius with articulating surfaces and 2.5 cm. of the shaft. Metal caps were placed on the bone stumps under the periosteum in 3 experiments. The specimens were examined 14, 28, 31, 87, 100, 105, 106, 129, 141, 143 and 146 days after operation (Fig. 2).



In 4 of the experiments the periosteal tube was closed separately. In 7 the periosteal tube was drawn together by closure of the overlying soft parts.

In 2 experiments in which the periosteum was closed, the continuity of the rib was found completely restored, after 100 and 143 days, respectively. The size and appearance of the regenerated rib were nearly normal. The periosteal tubes were dry when closed.

In the 100 days' experiment it is difficult to say whether the new bone was formed from periosteum or from the rib ends, as the continuity of the newly formed bone was complete. In the 143 days' experiment, however, in the center of the defect there was a definite transverse line of contact of two fragments, which seems to show that the growth was from the rib ends along the tube with final junction. If this supposition is correct, the growth must have been from the rib ends along the periosteal tube, because, if it had been from the periosteum itself, there would have been no such line of junction. (It might be said that this line may have represented a subperiosteal fracture of the newly formed rib with healing, but if this were the case the continuity of the rib must have been complete before the fracture.)

In 4 of the experiments the periosteal tube was not closed separately after removal of the section of the rib. In 2 of these the defect was filled with bone. In 1 of these experiments (146 days) the continuity of the rib was completely restored. The new bone was flatter and thinner than the normal rib, but was in good line. In the other experiment (105 days) the defect was filled with bone, but there was motion in the center. The new bone was shown by the X-ray to be definitely from the rib stumps. The ends had grown long enough to touch each other and had then overlapped, instead of joining solidly. The new bone growth was not as thick as the normal rib, and was not quite in line with the intact rib. The growth was thicker and longer from the vertebral stump than from the sternal fragment. Had the growth been from the periosteum, it would probably have been fairly uniform in thickness, and the overlapping would have been unlikely.

In 2 of the other rib experiments, where the periosteal tube was not closed separately, the defect was not filled with bone. In 1 of these, after 14 days, no new bone formation could be made out. In the other, after 87 days, there was a definite growth of bone from both rib ends, but not enough to fill the defect. This growth was thicker from the vertebral than from the sternal stump. If the growth of bone had been from the periosteum it would have been of the same thickness throughout the defect. It is impossible to explain why the growth of bone in the 87 days' experiment was relatively slower than in the 100 and 105 days' experiments.

Two of the radial experiments will be considered together. In one, 5.8 cm. of the shaft of the radius were resected. No especial care was taken to remove the fine particles of bone left at the muscle attachments. After 31 days the X-ray plate showed a narrow line of bone formation between the stumps. This was apparently along the line of muscle attach-

ment, where bone particles had probably been left. There was also bone formation from the radial stumps. Had the growth been from the periosteum alone, considering the size of the tube, it is probable that the growth would have been more extensive (Fig. 3).

In the other experiment the entire radius with its articular cartilages was removed. Especial care was taken to leave no particles of bone. After 129 days there was no bone formation demonstrable.

When we compare this experiment with the 31 days' experiment, it would seem to show that, unless bone particles are present in the periosteal tube after subperiosteal resection of bone, no bone is produced, except from the bone stumps.

In 3 experiments metal caps were placed over the stumps, inside the periosteal tube, in order to further test the bone-producing power of periosteum. Metal caps were placed on the rib stumps after subperiosteal resection of 1.5 cm. of a rib, and the periosteum was closed without blood-clot. After 28 days, no bone formation was present in the tube between the caps or around them.

In another experiment caps were placed on the stumps of the radius inside the periosteum, after subperiosteal resection of 2.5 cm. of the shaft. The tube was not sutured. There was no blood-clot. After 106 days the defect was found filled with a solid mass of bone, which impinged on the upper cap and spread out around it like an inverted mushroom. The lower fragment had been displaced laterally. The X-ray plate showed the growth of new bone to have formed from the side of the lower fragment, just below the cap, and to have followed the line of the tube. There was no growth of new bone around the upper cap.

In another experiment caps were placed on rib stumps after subperiosteal resection of 2 cm. of a rib. A blood-clot was placed in the tube and the periosteum was closed. After 141 days the continuity of the rib was found restored. The X-ray plate showed the caps in place. One of them was nearly surrounded by new bone and the defect was filled with new bone. Dissection showed the cap, which was not surrounded by bone, to be tilted outward, and the growth of new bone to have come from the side of the rib back of the cap. The new bone around the other cap seemed to have come from the rib behind the cap, but may have come partially from the periosteum. It is impossible to decide definitely (Fig. 4).

In the 106 days' experiment the new growth of bone was definitely from the side of the shaft of the lower fragment. In the 141 days' experiment the bone growth was, at one end, definitely from the rib behind the cap, while on the other end, in addition to growth from the rib behind the cap, it may probably have also had a periosteal origin. It is doubtful whether the blood-clot had anything to do with the bone formation. In the 28 days' experiment there was no attempt whatever at new bone formation between the caps and, if new bone was to be formed by the periosteal tube, it would probably have begun in four weeks.

The results with the metal caps confirm the idea that peri-



osteum alone without bone, even when its blood supply has been undisturbed, has not the function of producing new bone.

REMARKS.—The group shows that the periosteum acts only as a limiting membrane. In those experiments without metal caps where the periosteal tube was closed separately, the size of the new-formed bone was almost normal. In those in which the periosteal tube was not closed, the bone was somewhat irregular in shape. In none of the experiments could it be definitely demonstrated that the new bone was produced from the periosteum. The only instance in which new bone occurred along the periosteal tube was in the case of a resection of a portion of the radius, in which experiment no particular attention was given to the removal of bone particles from the line of muscle attachment. Even in this experiment the growth of bone was much more marked at the radial stumps. In the metal cap experiments the growth of bone was definitely from the shaft of the bone behind the caps, rather than from the periosteum.

#### GROUP IV.

##### THE TRANSPLANTATION OF BONE AND OTHER SUBSTANCES, INTO THE PERIOSTEAL TUBE AFTER PARTIAL SUBPERIOSTEAL RESECTION OF A RIB.

TYPICAL EXPERIMENT.—Fox terrier; about 10 months old. *Operation:* An intact auto-phalangeal bone was transplanted between the rib stumps, after subperiosteal resection of a portion of a rib. The periosteal tube was closed over it. After 107 days the continuity of the rib was found restored, and there was thickening in the region of the transplant. The transplant was adherent to the rib and new bone beneath it at one end, but was slightly movable at the other end. The X-ray plate showed general atrophy of the transplant. It had been pushed to one side by the growth of new bone, which was apparently from the rib ends.

SUMMARY.—Twenty-one experiments were done on dogs. The length of the sections of rib removed varied between 1.5 and 3 cm. The periosteum was closed over the transplant in 18 experiments, and the transplant was held in the periosteal trough by sutures in 3 experiments. Auto-bone with periosteum and without periosteum was used in two sets of 3 experiments. Iso-bone without periosteum was used in 10 cases. Auto-cartilaginous rib with perichondrium, cow's horn, dried iso-tendon, silver wire, and insoluble gelatin in 1 of each. The specimens were examined 24, 30, 31, 35, 44, 50, 92, 94, 100, 105, 107, 146, 206 and 215 days after operation.

Sections of auto-fibula, 2 cm. long, with periosteum, were placed between the rib stumps after the subperiosteal resection of two ribs. In one case the periosteal tube was closed over the transplant, and in the other the transplant was held in position by sutures. After 92 days the transplant over which the periosteum had been closed had grown firmly to the rib ends. There was slight thickening at its junction with the rib ends, but otherwise the size and shape of the bone was unchanged. The X-ray picture showed no attempt at bone growth from the periosteum outside the transplant. At the site of the other transplant, over which the periosteum had

not been closed, there was considerable thickening of the bone with slight motion at one end. The X-ray plate showed the transplant in position, but partly surrounded by new bone. A recent fracture at the junction of the transplant with the rib allowed the motion. The bone around the transplant may have been partially derived from the periosteum, but had apparently originated from the rib itself, and followed the periosteal tube.

A section of auto-cartilaginous rib without bone was placed between the rib stumps after subperiosteal resection of a portion of a rib. After 39 days we found thickening at the junction of the transplant with the rib ends. The X-ray picture showed irregular ossification of the cartilage and bone growth into it from the rib ends. There was also a line of bone from one rib end, held in by periosteum, which extended over the surface of the perichondrium.

In each of those experiments, including the typical experiment, in which the transplants were covered with periosteum, the growth of bone, wherever present, had originated from the rib ends, and not from the periosteum. The periosteum and cartilage of the intact phalangeal transplant had prevented the entrance of any new bone from the rib ends, and the transplant had been pushed to one side by the bone growth from the rib ends, as an impervious foreign body would have been. The periosteal covering of the other transplants had allowed the growth of bone to enter the transplant only from the ends. In those instances in which there was growth over the surface it ran between the periosteal tube of the rib and the periosteal covering of the transplant.

In 2 experiments auto-bone shavings with blood were placed in the defect made by subperiosteal resection of a portion of a rib. The periosteum was not closed in either instance. In both of these specimens, after 50 and 94 days, respectively, the defect was filled with an irregular mass of dense bone, which was solidly adherent to one rib stump. The X-ray plate showed definitely that but little of the growth was from the stumps. The bone shavings may have lived or, being in contact with the periosteum, may have stimulated it to bone formation; or both conditions may have occurred.

To compare with these experiments we transplanted iso-bone shavings with blood into the defect after subperiosteal resection of a part of a rib, and closed the periosteum over the mass. After 100 days there was thickening at the site of the transplant and free motion in its center. The X-ray picture showed the defect filled with solid bone, except in the center, where there was a transverse cleft. This bone had followed the periosteal tube, and was apparently from the rib ends. If the growth of bone had been from the periosteum, the chances are that its growth would have been continuous.

A section of auto-skull-bone was shaped and placed in a defect made by subperiosteal resection of a portion of a rib. The periosteum was closed over the transplant. After 35 days there was marked thickening of the rib in the resected area. There was solid union of the transplant to the rib stump at one end, but movement at the other. The X-ray plate showed the graft acting as a foreign body, surrounded by new bone.



There was a growth of bone from each rib stump, but the principal growth seemed to be from the periosteum. Microscopic examination showed no bone growth from the transplant, but marked degeneration. This suggests that auto-bone without periosteum, when placed in a periosteal tube, may stimulate periosteum to new bone formation.

In 2 experiments sections of 3 ribs were resected subperiosteally, with intact ribs between, and into each defect was placed a section of iso-rib without periosteum. The periosteum was closed over each transplant. After 31 and 44 days the continuity of the ribs had been re-established in all. One is struck by the great amount of bone production, which may have been due to the constant movement of the chest wall. It also suggests that iso-bone without periosteum in a periosteal tube may have the power to stimulate bone growth from the periosteum, as well as from the rib ends. Four of these transplants were acting as foreign bodies and were being surrounded by bone, while two were being incorporated in the new growth. Each transplant represented a different stage in the process. The 44 days' specimen was slightly further advanced than the 31 days' specimen (Fig. 5).

A piece of split iso-humerus without periosteum, 2.2 cm. long, was shaped and placed in a defect made by subperiosteal resection of a portion of a rib. The specimen was examined 100 days later. A piece of iso-radius without periosteum, 2 cm. long, was similarly treated. The specimen was examined 105 days later. In both the periosteum was closed over the transplant. In both the continuity of the rib was re-established. In the 100 days' specimen the X-ray picture showed the transplant to be still intact and continuous with the rib ends. It was surrounded by new bone, which seemed to be from the rib ends, and possibly also from the periosteum. In the 105 days' specimen the transplant could not be found. The rib was thickened and the continuity was restored, but the transplant had disappeared. It is impossible to say whether the bone growth was from bone ends or from the periosteum, or both. The new bone followed the periosteal tube. It is difficult to believe that such different pictures could be produced under such similar conditions, as to length of time, density of bone, etc.

As a control the following experiment was done: A section of radius, 2.3 cm. long, was removed subperiosteally. Metal caps were placed on the bone stumps under the periosteum. The periosteal tube between the caps was filled with bits of iso-bone. The tube was closed. After 24 days the X-ray picture showed the area between the caps to be solidly filled with dense bone, in which some of the individual grafts could be seen. Microscopic examination showed the grafts themselves to be dead. There was new bone closely joining the grafts, which in some places was from the edges of the grafts and probably also from the periosteum.

Several points of interest were noted: That both auto- and iso-bone without periosteum, when transplanted into the periosteal tube, after subperiosteal resection of a rib, had had a stimulating effect on new bone formation from the periosteum and also from the rib ends. The stimulation of bone

growth was much more marked than in the experiments in which periosteum was left on the transplant. That transplants of the same size under exactly the same conditions act quite differently, some apparently causing more stimulation than others. Some acted as a foreign body, some were undergoing absorption, some had disappeared, others were incorporated in the continuity of the bone. In no instance could new bone formation be demonstrated from the grafts themselves.

A piece of cow's horn and a section of dried iso-tendon were placed in the defects made by the subperiosteal resection of 2 cm. of two ribs. The periosteum was closed over the transplants. After 146 days the continuity of the ribs had been re-established. There was uniform thickening at the site of the transplants. The X-ray plate showed complete repair of the defect with absorption of the transplants. It is impossible to say whether the new bone was from the rib ends or from the periosteum.

A twisted piece of silver wire was placed in the defect made by subperiosteal resection of 2.4 cm. of a rib. The periosteum was closed over the wire. After 206 days the continuity of the rib had been restored. There was little thickening. The X-ray plate showed regeneration of the rib; the wire had been pushed to one side by the bone formation, which had gone on beneath it from the rib ends. Had the growth been from the periosteum the wire might have been surrounded by bone (Fig. 6).

A roll of insoluble gelatin was placed in the defect left by subperiosteal resection of 2.8 cm. of a rib. The periosteum was closed over it. After 215 days the continuity of the rib had not been restored; the gelatin was still present, and there was growth of bone from both rib stumps extending a short way into it. There had been no periosteal bone formation, and apparently none from the junction of periosteum and bone, where it is so frequently found.

In each experiment the periosteum was closed over the transplant. In only one was the defect not filled with new bone. This may have been due to the chemical structure of the gelatin. The new growth in each case was held in by the periosteal tube, and in each experiment the growth seemed to be from the bone ends rather than from the periosteum. The extrusion of the phalangeal bone with the formation of new bone from the rib ends beneath it, is very similar to the extrusion of the twisted silver wire by new bone formation. The cow-horn and dried iso-tendon transplants had been absorbed, and it was impossible to say whether the new bone formation was from the rib ends or from the periosteum.

REMARKS.—From this group of experiments we may conclude that either auto- or iso-bone, without periosteum, when they are transplanted into a periosteal tube after subperiosteal resection of a portion of a rib, will cause a very marked stimulation of bone growth, both from the rib ends and from the periosteum, in a comparatively short period of time. Transplants covered with periosteum, and also foreign bodies, seem to have no effect on the periosteum, but in each instance there was stimulation of growth from the rib ends.



## GROUP V.

## SILVER WIRE EXPERIMENTS.

**TYPICAL EXPERIMENT.**—Fox terrier; about 6 months old. *Operation:* A zone of periosteum, 2.5 cm. wide, was removed from the shaft of the humerus, and a double twist of silver wire was wrapped snugly around the center of this area. After 133 days the wire was visible throughout its entire extent. It had become loose and in places lay in a shallow groove, apparently due to absorption caused by the pressure of the wire on the bone. The X-ray picture showed no new bone formation.

**SUMMARY.**—Fourteen experiments were done on 8 dogs and on 6 rabbits. The femur was used in 6 experiments, the humerus in 5, and the radius in 3. In 7 experiments the silver wire was wrapped snugly around the bone after removal of the periosteum. The bone was curetted in 1 experiment; no precautions were taken against infection in 2, and in 1 of these the bone was also scraped. In 2 experiments the wire was placed over intact periosteum; in 1 over a fascia cuff, after removal of the periosteum; and in 1 subperiosteally. The zone of periosteum removed varied in width between 1 and 3 cm.

In 4 of the dog experiments the silver wire was placed around bone denuded of periosteum without disturbance of the bone itself. There was no new bone formation covering the wire, but rather an absorption ring under the wire, after 66, 91, 133 and 218 days. In 2 experiments the wire was placed over the intact periosteum, and a ring of absorption was present beneath the wire after 66 and 167 days. In 1 experiment the wire was placed around the bone as far as possible subperiosteally, and there was no new growth of bone after 167 days. In 1 experiment a cuff of fascia lata was sutured snugly around an area denuded of periosteum, and a wire ring placed over the fascia. After 66 days the specimen showed a slight constriction of the diameter of the shaft, due to the pressure of the snug fascia band (Fig. 7).

In 3 of the rabbit experiments the specimens were examined 44, 48 and 54 days after operation, and these can be grouped as to time. In no experiment was the wire covered by new bone for more than one-fourth of its length. In each experiment there was more bone growth posteriorly in the region from which the muscle attachments had been torn. In 1 experiment the loop was not covered in this region; in 1 it was covered by a thin plate of bone, through which it could be seen, and in 1 experiment it was buried in a thick, bony ridge. In the experiment in which no precautions against infection were taken, after 48 days a shallow ring of new bone had extended nearly all around the shaft, although it did not cover the loop.

In 3 other rabbit experiments, which can also be grouped as to time, the specimens were examined 121 and 122 days after operation. In 1 experiment, in which no precautions had been taken against infection, all but the twist and about one-sixth of the loop was covered by a thin layer of bone, through which the wire could be seen. In 1 experiment, in which the bone was roughly curetted, the twist and about one-

fourth of the loop was still uncovered after 122 days. The remaining three-fourths of the loop was covered by a thin layer of bone, except posteriorly, where it was buried in a thick ridge of bone. This was simply an advanced stage of the 48 days' experiment spoken of above, which was carried out under similar conditions. In 1 experiment in which the bone was undisturbed after removal of the periosteum, the wire was visible everywhere, after 121 days, except posteriorly, where a thin band of new bone covered it. At several points around the shaft a slight ring of new bone had formed, but not as high as the wire loop (Fig. 8).

There was no visible thickening of the area from which the periosteum was stripped in the dog experiments, but there was definite thickening over this area in each instance in the experiments on rabbits. In fact, there seemed to be a somewhat greater tendency to bone growth in the rabbits in this group than in the dogs.

One is struck by the fact that the most extensive growth of new bone around the wire occurred in the experiments in which no precautions were taken against infection, and also in which the bone was curetted after removal of the periosteum. The thickest growth was always posteriorly, in the region from which the muscle attachment had been torn, or, in other words, where the bone has been most traumatized.

From these experiments we are led to believe that there is little if any new bone formed from the surface of a bone, after removal of the periosteum, unless the bone surface itself is irritated, either mechanically or by infection. That absorption occurs when silver wire is snugly applied around bone over intact periosteum, and also at times when around the denuded bone. That there is little if any new bone formation from the periosteum or bone, when a silver wire is placed around a bone subperiosteally. Thus it would seem that, in those experiments reported by others in which the ring was completely buried in new bone, either there was infection, or that the surface of the bone was much traumatized after, or during, the removal of the periosteum.

Clinically, I have noted that, when bones had been sutured with silver wire, there was usually absorption beneath the wire, rather than new bone formation over it.

## GROUP VI.

## THE IMPLANTATION OF BONE AND ALSO PERIOSTEUM INTO PREPARED DEFECTS IN THE SKULL.

**TYPICAL EXPERIMENT.**—Mongrel dog; about 5 months old. *Operation:* After removal of the periosteum a button of bone 2 cm. in diameter was taken from the left temporal region. Into the defect were placed small bits of auto-rib which had been thoroughly scraped to remove all periosteum. After 35 days the defect was practically filled with a rigid crust of bone. The individual grafts could be plainly seen by transmitted light. X-ray and microscopic examination showed bone proliferation from the edges of the defect, and also from a number of the transplants. In several places there was solid junction between the edges and the grafts.



SUMMARY.—Nine experiments were done on dogs. In 2 experiments auto-periosteum was transplanted; in 4, split auto-rib without periosteum; in 1, auto-rib cut into bits; in 2, split iso-rib was used. In 1 experiment the defect was made with a trephine, and in 8 with the Hudson burr. The diameter of the defects varied between 1.1 to 2 cm. The transplants were placed on the dura in each instance.

The specimens were examined 35, 49, 93, 105 and 146 days after operation. In 2 experiments auto-periosteum was transplanted. In the 93 days' specimen there was a definite shadow on the X-ray plate, and microscopic examination showed bone formation. This periosteum had been roughly scraped from a rib, and may have had bone particles attached to it. The other periosteal transplant (49 days) was carefully removed, having no bone particles attached. In this experiment there was no bone formation. In both of these experiments there was bone growth from the edges of the defect.

In 2 experiments split iso-rib was transplanted, and in a corresponding opening on the other side of the skull split auto-rib was placed. In the 105 days' specimen the openings were entirely filled with bone, although by transmitted light the bone in some portions was much thinner than in others. The outline of the original grafts could be seen, and were firmly adherent to the edges of the defect and to each other. In the 146 days' experiment the defects were more solidly filled with bone, and there was less space between the grafts. The grafts themselves had been replaced by new bone. As to the clinical result after closing the defect, there was little to choose between the auto- and the iso-transplants.

In 2 experiments where split auto-rib without periosteum was used, the grafts were firmly attached to the edges of the defect, after 49 and 93 days. There was little, if any, proliferation of bone from the sides of the long strips. There was, however, proliferation of bone from the shorter strips, which had grown together and joined the longer strips. There was proliferation of bone from the edges of the defects. The grafts were apparently intact.

In 1 experiment small bits of auto-rib were placed here and there over the dura. After 35 days the defect was filled with bone. The X-ray picture showed proliferation of bone from the grafts and from the edges (Fig. 9).

These experiments show that transplants without periosteum retained their vitality, and that there was proliferation of bone from them, as well as from the edges of the defects. This was especially noticeable in the small fragments, as there was comparatively a much larger raw surface and consequently a better blood supply. The new bone seemed to come from the cut surfaces, rather than from the surface from which the periosteum was stripped. In 1 experiment there was new bone found in a periosteal strip which had been scraped from a rib (thus making the presence of bone particles possible), but in another experiment, where there was positively no bone attached to the periosteum, no new bone was formed. In 2 experiments where iso-grafts without periosteum had been transplanted, the outlines of the grafts were still present after 105 and 146 days. The transplants had been replaced by new

bone from the edges following the line of the grafts. The stimulation of the edges of the defect seemed as great where iso-bone was transplanted as when auto-transplants were used; the closure of the defect was equally good in each.

## GROUP VII.

### AUTO-BONE IN SOFT PARTS.

TYPICAL EXPERIMENT.—Mongrel dog; about 1 year old. *Operation:* A section of rib, 2.9 cm. long, was removed subperiosteally and was transplanted between the ribs and the overlying muscle. After 206 days the bone was found snugly surrounded by connective tissue. It was much shorter and thinner than when transplanted, and had an irregular outline. The X-ray plate showed absorption everywhere, but much further advanced in some places than in others.

SUMMARY.—Twenty-five experiments were done. In 8, the bone was transplanted with its periosteum; in 17, without periosteum. In 11, sections of the ribs were used; in 4, portions of the radius; in 7, sections of the fibula; in 2, bone shavings from the skull, and in 1, an intact phalangeal bone. The bone fragments varied in length between .5 and 3 cm. The specimens were examined 11, 14, 19, 20, 55, 67, 94, 100, 104, 108, 113, 127, 128, 141, 143, 147, 206 and 207 days after operation.

There was little change in the transplants up to two weeks. After 19 days cross-sections of radius, .5 cm. long, without periosteum, both in subcutaneous tissue and in muscle, showed about the same degree of beginning absorption. After 20 days there was no sign of absorption shown by the X-ray picture in a section of the shaft of the fibula, 2.8 cm. long, with its periosteum, in muscle tissue. A section of auto-rib without periosteum, 1.5 cm. long, was sutured end to end to the stump of a cartilaginous rib, in which there was no bone. After 30 days the length was the same as when transplanted, but it was not quite so thick. The X-ray plate showed absorption from the edges.

A section of the shaft of the fibula, 3 cm. long, with its periosteum, was as flexible as a piece of rubber after 67 days. It was somewhat shorter than when transplanted, and about one-fourth as thick as the control fibula. This is very noticeable in the X-ray plate.

A section of rib without periosteum, 2.5 cm. long, was split into 4 pieces, which were placed side by side in muscle. After 100 days all of these pieces had joined in an irregular mass, and there had been growth of bone from the ends, and from several places in the length of the fragments. This framework of bone was rigid, but was very thin and almost transparent (Fig. 10).

Bone shavings from the skull mixed with blood had completely disappeared after 55 and 94 days.

A piece of split radius, 2 cm. long, without periosteum, placed in the subcutaneous tissue, had disappeared after 104 days. A section of rib, 1.8 cm. long, with a strip of periosteum, in muscle, had been absorbed after 108 days. An intact phalangeal bone, placed in muscle, still showed its out-



line in the X-ray plate, but was very thin and almost transparent, after the same length of time.

A section of the shaft of the fibula, 1.6 cm. long, without periosteum, was put in a blood-clot, and the mass was placed in a pocket in the subcutaneous tissue. The bone was found encapsulated 113 days later, but was much smaller and evidently undergoing absorption.

Two pieces of auto-rib, each 1.8 cm. long, without periosteum, were placed side by side in the subcutaneous tissue. After 127 days the fragments were found grown firmly together in an irregular mass. There was new growth of bone from one end of one fragment to the middle of the other. The transplants were very thin and nearly transparent. There had evidently been marked absorption going on also. When we compare this with the 100 days' experiment, we find the same picture, although the thickness of the specimen, where the whole thickness of the rib was used, was no greater than where the split rib was used.

A section of the shaft of the fibula, 1.2 cm. long, with its periosteum, was placed in the subcutaneous tissue. After 128 days a small portion of the bone was still present, although it was flexible and did not cast a shadow with the X-ray.

A section of the shaft of the fibula, 3 cm. long, with its periosteum, was removed. The periosteum was rolled back from each end for 1 cm., and 1 cm. of bone was cut off from each end, thus leaving 1 cm. of bone in the middle covered with periosteum. The cuffs of periosteum were then drawn up over the ends of the bone and twisted, so that the ends of the bone were also covered. This piece with periosteum, and the other two pieces of the same length without periosteum, were placed in muscle tissue. After 128 days the fragment covered with periosteum was rigid and apparently intact, except for slight rounding of the ends. The two other pieces were flexible and shorter, and showed evidences of absorption (Fig. 11).

A section of rib, 2 cm. long, without periosteum, in muscle, was almost absorbed in 141 days, only a tiny bit of bone remaining, which was also in process of absorption.

Two pieces of the shaft of the fibula, 1 cm. long, with periosteum, were still present after 141 days. The fragments were much smaller and showed marked evidence of absorption.

A section of rib, 1 cm. long, without periosteum, was surrounded by omentum, and 143 days later only a tiny bit of the bone remained. A section of rib of the same length, placed between peritoneum and muscle, had been absorbed in the same length of time. A section of rib, without periosteum, in the subcutaneous tissue, had evidently been absorbed after 147 days.

Two sections of rib, 1.8 cm. long, without periosteum, placed in muscle tissue, had been entirely absorbed in 207 days, while another section of rib, 2.9 cm. long, without periosteum, placed between muscle and ribs, could still be found after 207 days, although considerable absorption had taken place.

REMARKS.—It is a difficult matter to draw conclusions from this group of experiments, as in some instances the findings seem to contradict each other. Those experiments, in which the bone was transplanted without periosteum, present very

different pictures. Beginning absorption was noted as early as the 19th day. A section of rib, 2 cm. long, had disappeared in 104 days. On the other hand, portions of almost transparent bone were still present after 113, 128, 141, 143 and 207 days, whereas transplants of the same size in the same animals were absorbed in the same length of time. The rib transplants became flexible. In 3 experiments the transplants were placed close together. In 2 of these where sections of the whole rib in subcutaneous tissue and split rib in muscle were used, there was a definite new growth of bone and growing together of the fragments, but at the same time there were marked absorptive processes going on, and the resulting mass was as thin as paper and almost transparent. When 2 pieces of the fibula were placed side by side in muscle no such growth was noted.

Those experiments, in which the bone was transplanted with its periosteum, seem to show that the periosteum had a certain protective action on the transplant. Sections of fibula without periosteum had markedly softened and been reduced in size after 128 days, while a control section of fibula covered with periosteum remained practically intact after the same length of time. A section of rib with a strip of periosteum had been absorbed in 108 days, whereas an intact phalangeal bone was still present after the same length of time, although reduced in size.

In practically all of the transplants which remained at the time of examination there were signs of absorption, which were more or less marked. In only 2 of the entire group had there been any attempt at new bone formation, and even in these marked absorption was also going on. The transplants covered with periosteum seemed to be somewhat more resistant to absorption than those without periosteum. There was little difference in result, whether the transplants were placed in muscle or in subcutaneous tissue.

The blood supply probably has a good deal to do with the length of time a transplant can remain in soft parts without absorption. The type of bone used may also have some bearing on this point, a porous bone being easier to nourish than solid bone. If this were an important point, it would seem likely that the bone shavings with blood would have survived better than the solid pieces.

From the above experiments we feel justified in saying, that in the large majority of cases absorption takes place when a transplant of auto-bone, either with or without its periosteum, is placed in soft parts. We cannot say what would be the fate of those transplants which have grown together and produced new bone but, as absorption was going on in the bone and as the tendency of free bone in soft parts is to be absorbed, it seems logical that absorption would eventually have taken place. The lack of function probably also has a definite effect on ultimate absorption.

#### GROUP VIII.

##### ISO-BONE IN SOFT PARTS.

TYPICAL EXPERIMENT.—Mongrel dog; about 18 months old. *Operation:* A section of iso-radius, 2.4 cm. long, with its periosteum was placed in muscle tissue. After 151 days



the bone was still present, but considerably shortened. The X-ray plate showed that the portion covered with periosteum was still quite clear-cut in appearance, but that marked absorption was going on at each end.

**SUMMARY.**—Nine experiments were done. In 3 the bone was transplanted with its periosteum, and in 6 without the periosteum. In 4 the radius was used; the rib and the skull each in 2, and the fibula in 1. The longest bone fragment was 2.4 cm.; in 1 instance bone shavings were transplanted.

The specimens were examined 11, 13, 33, 74, 93, 100, 145, 147 and 151 days after operation. The transplants were placed in the subcutaneous tissue in 5 instances; in the muscle in 3, and in the abdominal cavity in 1 instance. Bone chips without periosteum from the radius, in subcutaneous tissue, had entirely disappeared after 100 days. Bone shavings from the skull, in subcutaneous tissue, had been absorbed after 93 days. A section of rib, 2.2 cm. long, without periosteum, in subcutaneous tissue, showed an area of liquefaction with only a very small portion of the bony structure remaining after 74 days. A cross-section of radius, 2.2 cm. long, with periosteum, in muscle, showed evidences of absorption from the ends after 33 days. A cross-section of radius, 2.4 cm. long, with periosteum, in muscle, was still present after 151 days, although there was considerable absorption, especially marked at the ends, while the area covered by periosteum was in much better condition. A split fragment of radius, 2 cm. long, without periosteum, in subcutaneous tissue, was still present after 145 days, although absorption was going on. A button of bone from the skull 2 cm. in diameter, including both tables, had been completely absorbed after 147 days.

**REMARKS.**—It is again difficult to draw definite conclusions in this group, except that absorption takes place, which would probably eventually lead to complete disappearance of even the transplants in fairly good condition.

A cross-section of the radius, with periosteum, showed beginning absorption from the ends after 33 days, whereas another section of the radius, with periosteum, was in a good state of preservation 151 days after transplantation, except that considerable absorption had taken place from the ends. The periosteum seemed to have some power of preventing absorption when it remained attached to the bone. On the other hand, a piece of split radius, without periosteum, was still present after 145 days, although absorption was progressing. In no instance was there any attempt at new bone formation from the transplants.

#### GROUP IX.

##### AUTO-BONE IN BONE DEFECT.

**TYPICAL EXPERIMENT.**—Mongrel dog; about 1 year old. *Operation:* A section of the shaft of the fibula, 2.8 cm. long, was excised, and into this defect was placed 2.8 cm. of rib without periosteum. No attempt was made to hold the fragments in apposition. After 87 days the defect seemed to be solidly filled, but there was slight motion at the upper end of the transplant. The X-ray plate showed the transplant to

be considerably smaller in diameter. It was continuous with the lower fragment, where there was thickening. It had evidently been in contact with the upper fragment, but was not adherent, there being a false-joint formation. Microscopic examination showed an area of dead bone and some absorption, but as a whole vigorous, healthy bone.

This experiment shows that the transplant tends to assume the size of the bone into which it is transplanted. Also that the transplant lives and becomes a part of the host. There is little doubt but that the upper end would also have become firmly attached to the fibula, had the fragments been held in apposition.

**SUMMARY.**—Eight experiments were done on dogs. Defects were prepared in the radius in 2; in the fibula in 4; and in the humerus and femur each in 1 case. The periosteum was removed with the bone in each experiment. The resected bone varied between 1.4 and 4 cm. in length. The transplants were from the rib in 3; from the fibula and radius each in 2 cases, and from the femur in 1. They were without periosteum in 5, and with periosteum in 3. The specimens were examined 16, 64, 87, 92, 113, 130, 144 and 152 days after operation.

The periosteum was removed from the circumference of the femur, and an area of bone, 1.5 x .75 cm. long, was excised down to the marrow cavity. The bone was cut into small bits and was replaced in the defect, being held in position by a cuff of fascia lata, which was sutured snugly around the bone. After 130 days the bone under the fascia lata was definitely smaller than the corresponding area of the other femur. In one or two places the outline of the individual fragments could be seen, but the mass was flush with the surface of the bone, and had healed solidly in place. The fascia bundles, which had been purposely placed across the bone, could be plainly seen, and the fascia was more snugly adherent to the bone surface than was the adjacent periosteum.

This experiment shows that small fragments of bone, when replaced in a defect and prevented from extending beyond the surrounding bone, will heal smoothly into place. In this instance the fascia lata cuff acted as the limiting membrane. Fascia lata might be utilized, where periosteum is destroyed and overgrowth of bone is undesirable, as after operative work around joints.

A section of the shaft of the radius, 3.5 cm. long, was resected with its periosteum. The periosteum was removed thoroughly and the bone was cut into bits, which were placed in the muscle trough between the stumps. After 144 days the continuity of the radius was found to be re-established through an irregular mass of solid bone. There was compensatory thickening of the ulna, with a slight curve opposite the defect. The radius operated upon was .5 cm. shorter than the control. The X-ray plate showed atrophy of the upper fragment of the radius, with only slight proliferation from the stump. The lower fragment was normal, and there was a considerable amount of bone proliferation from the stump. There was bone formation around the bits of bone, which were solidly bound together.



The defect was filled with an irregular mass of solid bone which, while it conformed in a general way to the line of the bone, was not as thick as the shaft. There was atrophy of the upper fragment, which was probably due to interference with the artery. The transplants without periosteum had lived, and new bone formation had taken place around them. There was also new bone from the end of the lower stump, but not from the sides, as was the case in some instances in which the periosteum had been stripped back.

A section of the right radius, 1.5 cm. long, was resected with its periosteum. The periosteum was carefully removed and the bone was cut into bits. Some of the fragments were placed in a tube made of fascia lata. This tube was inserted into the defect, and the ends were drawn up like cuffs over the stumps and secured. After 152 days the defect was found filled with a mass of bone, which did not extend beyond the bone edges. Several of the bone fragments could be seen when the soft parts were removed. The lower radial stump was displaced posteriorly. There was compensatory thickening and also bowing of the ulna. The X-ray picture showed a number of the bone fragments still present, although some had been absorbed. Bone proliferation was slight from the grafts, although they were tightly bound to each other. There was some bone proliferation from both stumps.

In this experiment there was not much growth of bone from the radial stumps. Some of the grafts had survived, even though surrounded by a tough membrane, which would have interfered with the blood supply, for a time at least. The marked thickening of the ulna, to take care of the added weight, was noticeable.

The results from these experiments point to the fact that auto-grafts without periosteum, when cut into small bits, will live when placed in bone defects, and will produce new bone, which binds them together and also to the bone into which they are transplanted.

A section of the shaft of the humerus, 1.4 cm. long, with its periosteum, was excised, and to fill the defect a resected portion of a rib, 4 cm. long, without its periosteum, was forced into the marrow cavity of each fragment. The rib was not secured by pins, as the natural curve seemed to hold it firmly in place. The specimen was examined 16 days later. The rib had slipped from the lower fragment, but was tightly adherent to the upper fragment. The fragments were bound together quite firmly by a mass of callus. The X-ray plate showed no proliferation of bone from the cut surface of the lower fragment, although callus had already begun to form. A mass of callus was present around the transplant.

This illustrates the celerity with which new bone is formed and the remarkable strength of the healing of the fragments together, within this short time, in spite of the overlap. This overgrowth was probably due to the constant movement and irritation of the fragments.

A section of the shaft of the fibula, 4 cm. long, with its periosteum, was removed. Into the defect were placed two pieces of rib, each 2 cm. long. No attempt was made to hold the fragments in apposition. After 92 days the X-ray

plate showed the defect to be filled, except for 3 mm., between the lower fragment and the transplant. The outline of the bone was somewhat irregular and the transplants had assumed the size of the fibula. It was difficult to make out the point of junction of the upper fragment and the transplant, and also where the transplants had joined. The lower portion of the lower transplant had been absorbed. Microscopic examination showed a few small areas of dead bone; elsewhere there was healthy, growing bone.

This experiment shows that two long transplants placed end to end in a bone defect will grow together, as well as do the tiny bits of bone previously mentioned.

A section of the shaft of the fibula, 3.5 cm. long, with its periosteum, was excised. After removal of a strip of the periosteum with some bone, the section was turned upside down and replaced. After 64 days the fragment was found healed in position and the continuity of the fibula was restored. The X-ray plate showed thickening of the ends of the stumps and the transplant at the point of junction. The transplant was somewhat irregular and thicker than the normal bone. There was firm healing at the lower junction. The line of healing could be seen at the upper junction, although there was no motion.

A section of fibula, 2 cm. long, with its periosteum, was removed. Then bone was broken in three places without complete severance of the periosteum. It was then replaced upside down. After 113 days the continuity of the bone was found restored. The X-ray plate showed the inverted bone to be thicker and more irregular than the normal fibula. The line of fractures and junction with the fibula could not be made out (Fig. 12).

REMARKS.—These experiments show that auto-bone, both with and without periosteum, may be successfully transplanted to fill defects in bone. Tiny bits, or one single piece, may be used. The transplant tends to assume the size of the bone into which it is transplanted.

#### GROUP X.

##### ISO-BONE IN BONE DEFECTS.

TYPICAL EXPERIMENT.—Mongrel dog; about 8 months old. *Operation:* A section of the shaft of the radius, 3 cm. long, with its periosteum, was removed, and into the defect was placed a section of radius of the same length, without periosteum. After 121 days healing was complete, but the bone was shortened 1 cm. There was bending and thickening of the ulna opposite the defect. The X-ray plate showed the defect to be filled with irregular new bone from the bone ends, but the transplant had been absorbed.

SUMMARY.—Seven experiments were done on dogs. The defects were prepared in the radius in 6 experiments, and in the fibula in 1. The periosteum was removed with the bone in each experiment. The resected bone varied between 1.8 and 3 cm. The transplants were obtained from the radius in 5, and from the rib and fibula in 1 case each. The specimens were examined 20, 27, 29, 74, 121, 123 and 126 days after operation.





FIG. 1.—A pedunculated flap of periosteum with a thin film of bone was raised from the femur, and also from a rib. The soft parts were sutured beneath them. A. X-ray taken 34 days later. B. X-ray taken 50 days later.

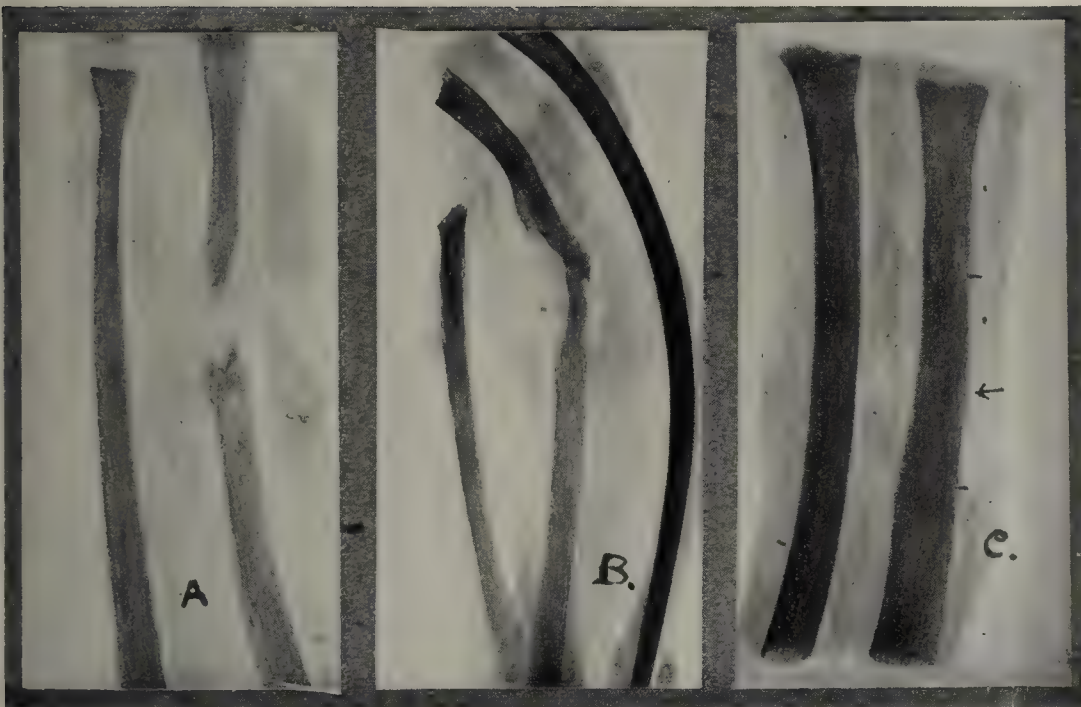


FIG. 2.—A. 87 days after operation. Extent of regeneration of a rib after a partial subperiosteal resection of 2.8 cm. The growth is only from the rib ends.  
B. 105 days after operation. Extent of regeneration of a rib after partial subperiosteal resection of 2.1 cm. The irregular growth is from the rib ends. The periosteal tube was not closed in either A or B.  
C. 100 days after operation. The regenerated rib after partial subperiosteal resection of 3 cm. The periosteal tube was closed and the growth has evidently followed the tube.



FIG. 3.—A. A section of radius, 5.8 cm. long, was excised subperiosteally. No attempt was made to remove tiny particles of bone, which may have adhered to the line of muscle attachment. X-ray taken 31 days later.  
B. The entire radius including the articulating surfaces was excised subperiosteally. No visible bone particles were allowed to remain. X-ray taken 129 days later.  
C. Control.



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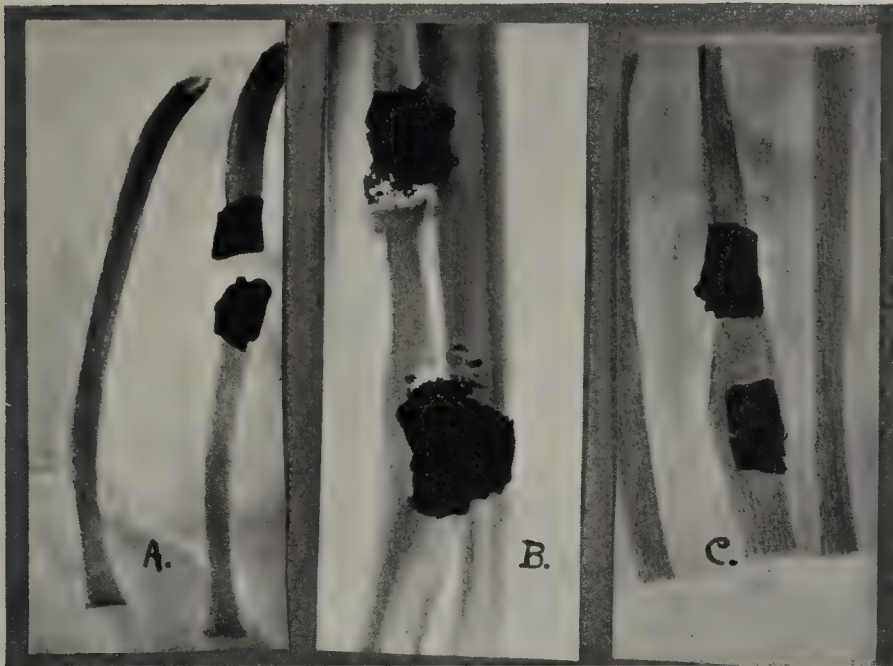


FIG. 4.—A. Metal caps placed on the stumps, after subperiosteal resection of 1.5 cm. of a rib. The tube between the caps was dry. The periosteum was closed over the caps. X-ray taken 28 days later.  
 B. Metal caps placed on stumps after subperiosteal resection of 2.5 cm. of shaft of radius. The tube between the caps was dry. The periosteum was not closed. X-ray taken 106 days later.  
 C. Metal caps on the stumps after subperiosteal resection of 2 cm. of a rib. A blood-clot was placed in the tube between the caps, and the periosteum was closed. X-ray taken 141 days later.  
 In A there is no attempt at bone formation from the periosteum. In B the new bone has formed from the side of the shaft back of the cap. In C the same thing has occurred, although the X-ray from above does not show it.



FIG. 6.—A. A piece of dried iso-tendon (1) and a piece of boiled cow's horn (2), were placed in defects made by the subperiosteal resection of 2 cm. of two ribs. The periosteum was closed over the transplants. X-ray 146 days later.  
 B. A piece of twisted silver wire was placed in a defect made by the subperiosteal resection of 2.4 cm. of a rib. The periosteum was closed over the wire. X-ray 206 days later.

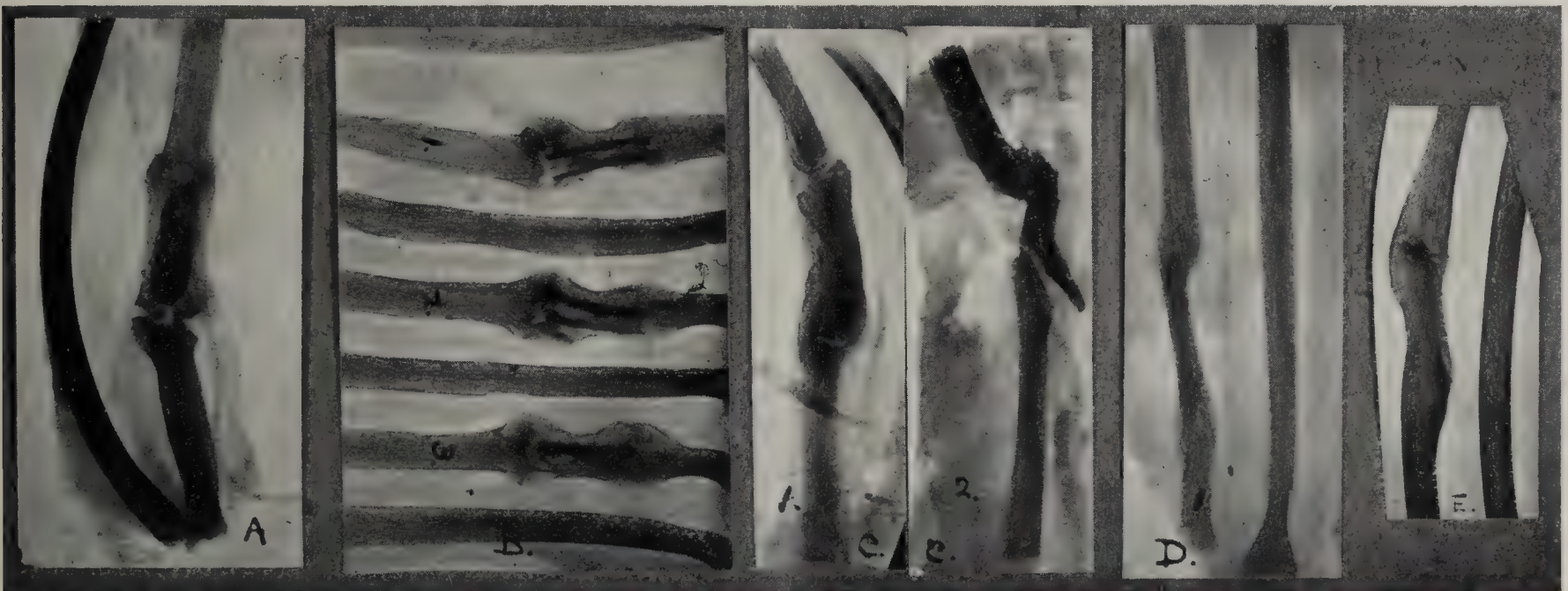


FIG. 5.—A. Auto-skull-bone, without periosteum, in defect left by subperiosteal resection of 2 cm. of a rib. The periosteum was closed. X-ray 35 days later.  
 B. Sections of iso-rib, without periosteum, in defects left by subperiosteal resection of portions of 3 ribs. The periosteum was closed over each. X-ray taken 44 days later.  
 C. Auto-bone shavings with blood in defect after subperiosteal resection of a rib. The periosteum was not closed in either experiment. X-ray after (1) 50 days; (2) 94 days.  
 D. Auto-fibula with its periosteum in the defect, after subperiosteal resection of 2 cm. of a rib. The periosteum was closed over it. X-ray taken 93 days later.  
 E. A split piece of iso-humerus without periosteum put into the defect after subperiosteal resection of 2.2 cm. of a rib. The periosteum was closed over the transplant. X-ray 100 days later.



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FIG. 7.—Silver wire experiments on dogs. *A.* The upper wire was placed over intact periosteum; the middle wire was placed over a cuff of fascia lata, after removal of the periosteum; the lower wire was placed over denuded bone. X-ray 66 days later. *B.* The upper wire was placed over undisturbed periosteum; the lower wire around the bone subperiosteally. X-ray 167 days later. Silver wire around denuded bone. *C.*, after 91 days. *D.*, after 133 days. *E.*, after 218 days.

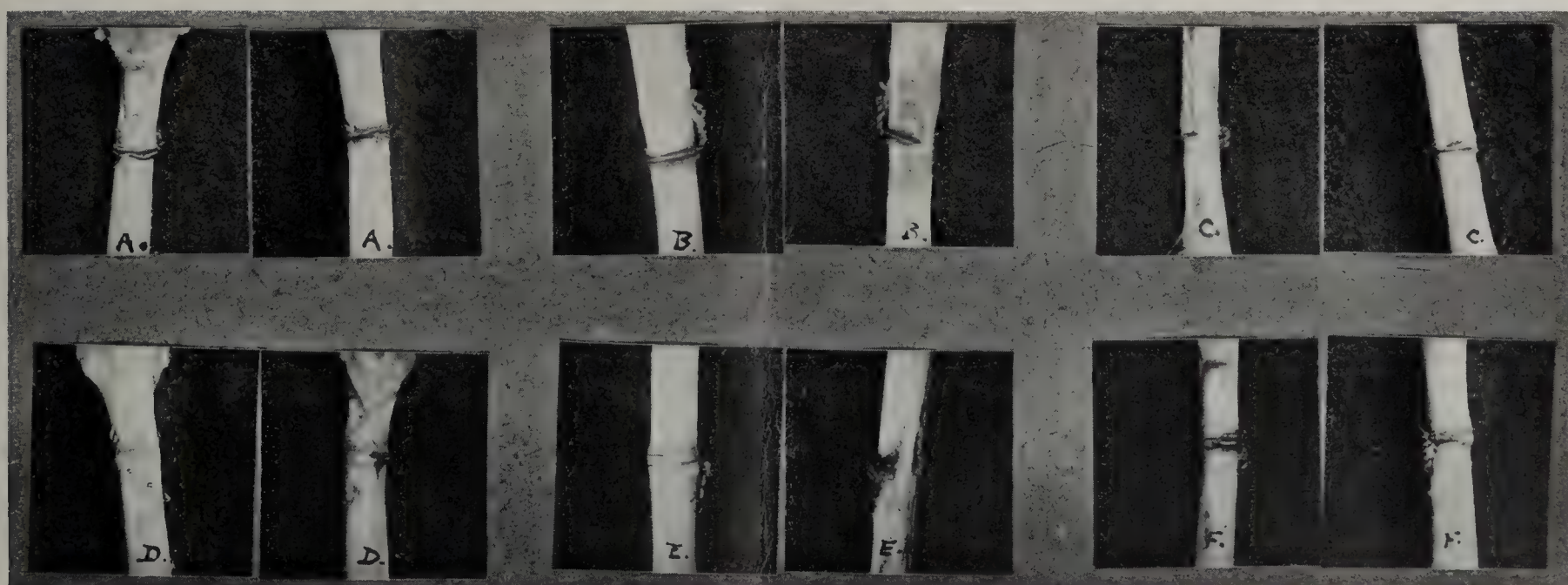


FIG. 8.—Silver wire experiments on rabbits. Front and back views. Silver wire was placed around the femur, after removal of zones of periosteum from 1.5 to 4 cm. wide. *A.*, after 44 days. *B.*, after 48 days. *C.*, after 54 days. *D.*, after 121 days. *E.*, after 122 days. *F.*, after 122 days. In *A* and *D* no precautions were taken against infection. In *E* the bone was curetted before the wire was applied.



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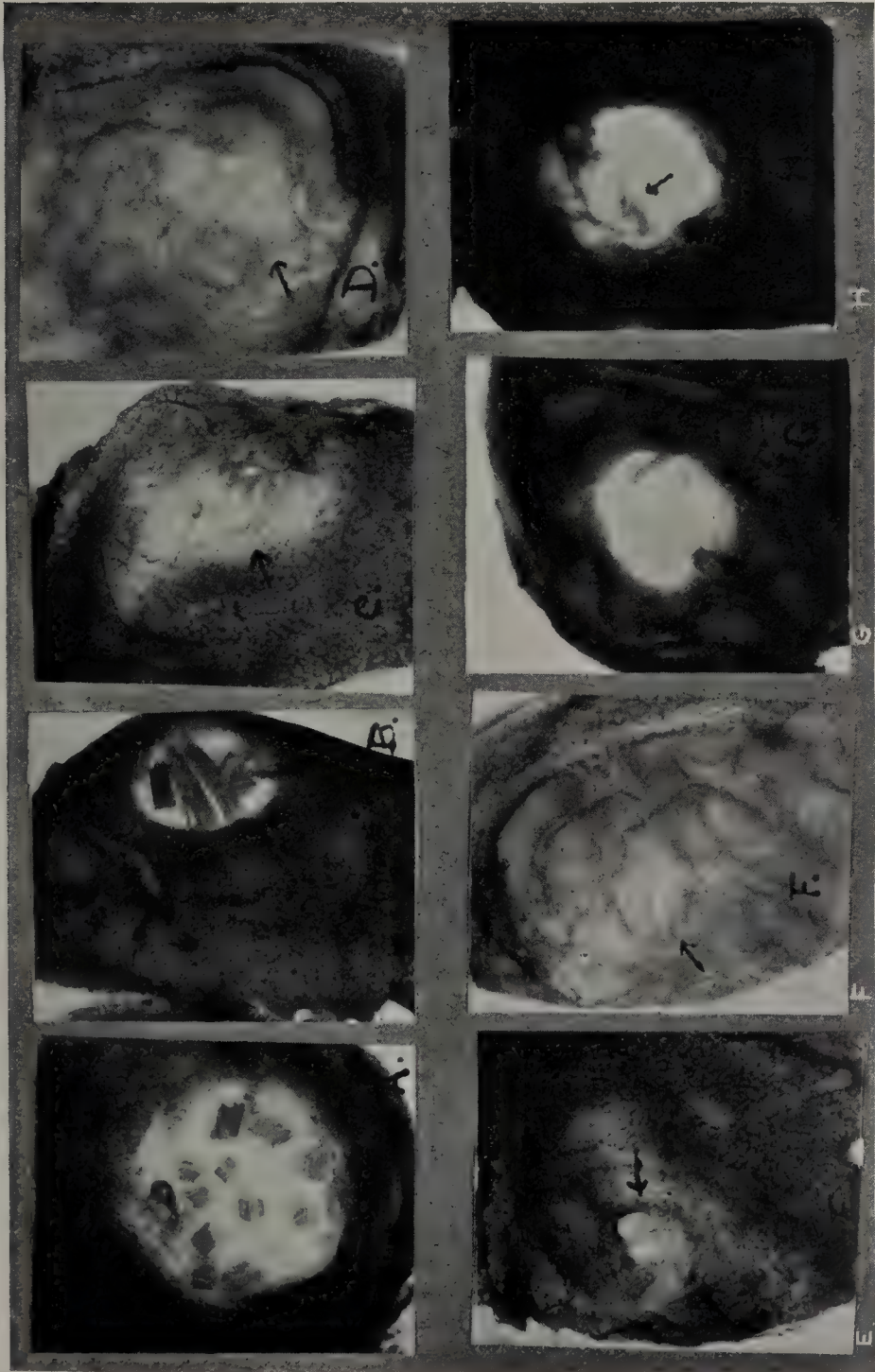


FIG. 9.—Split auto-rib without periosteum in skull defects. A, after 49 days. B, after 93 days. C, after 105 days. D, after 146 days. Split iso-rib in skull defect. E, after 105 days. F, after 146 days. Auto-periosteum in skull defects. G, after 49 days. H, after 93 days.

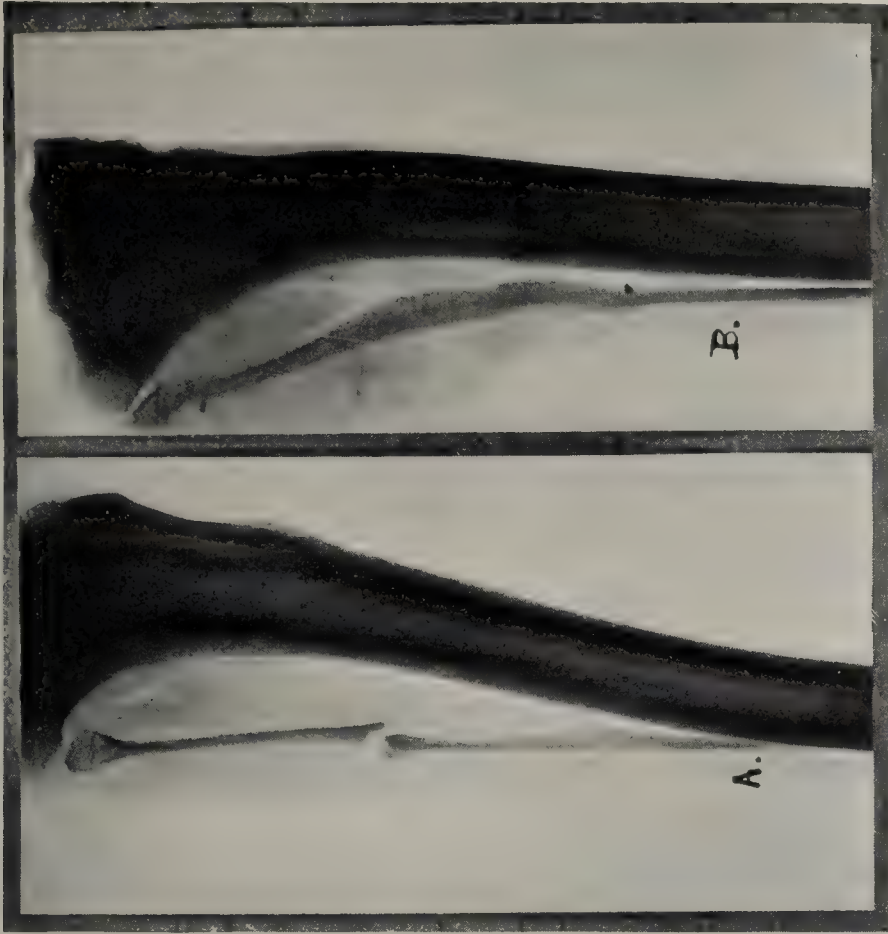


FIG. 12.—A. A section of auto-rib, 2.8 cm. long, without periosteum was placed in a defect of the same length in the fibula. X-ray 87 days later. B. A section of fibula, 2 cm. long with its periosteum, was removed. It was broken into 3 pieces transversely without entire severance of the periosteum, and was replaced upside down. X-ray 113 days later.



FIG. 11.—A. Sections of auto-rib, each .75 cm. long, were placed on a denuded rib. 1 was covered with periosteum; 2 was denuded. The wound became infected. The transplant covered with periosteum is still clear cut and has resisted absorption much better than the transplant without periosteum. X-ray 20 days later. B. A section of auto-rib, 3 cm. long, was excised, and the periosteum was stripped back from each end. 1 cm. of denuded bone was cut off from each end. The periosteum was then drawn over the ends of the undisturbed portion, and twisted, the transplant being thus entirely covered with periosteum. The 3 pieces were then buried in muscle. 1. The specimen covered with periosteum was rigid and intact, except for absorption at the ends. 2. The 2 pieces without periosteum were flexible and showed evidences of absorption. X-ray 128 days later. C. An intact auto-phalangeal bone was placed in the soft parts. X-ray 108 days later. D. A section of auto-rib, 2.9 cm. long, was placed in the soft parts. X-ray 206 days later.

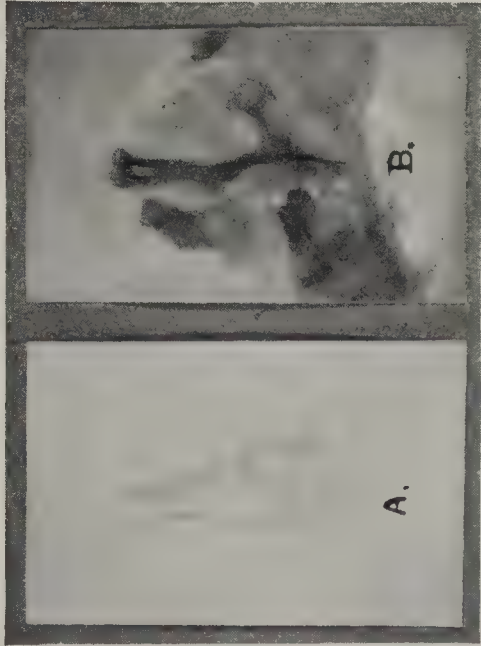


FIG. 10.—A. A piece of auto-rib, 2.4 cm. long, without periosteum, was split into 4 pieces which were placed side by side in the soft parts. X-ray 100 days later. B. Two pieces of auto-rib, 1.8 cm. long, without periosteum, were placed side by side in the soft parts. X-ray 127 days later.



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In 2 experiments the transplants were covered with periosteum. In 1, after 20 days, the transplant seemed intact, and there was quite firm union with the upper fragment. The X-ray plate showed the growth to be from the upper fragment. In the other, after 29 days, the transplant was intact and firmly adherent. The X-ray plate showed marked proliferation of bone from the sides and cut surfaces of both radial stumps, and a definite attempt to surround the transplant with new bone. There was no proliferation of bone from the transplant, and no evidence of absorption. These animals died of pneumonia, so that the specimens were examined sooner than was intended.

One experiment, in which the transplant was not covered with periosteum, may be compared with that just described. After 27 days the transplant was found to be tightly adherent to the upper radial stump. The X-ray plate showed slight proliferation of bone from the radial stumps and possibly a slight thickening of the side of the transplant. The growth of bone from the radial stumps was much more marked in the specimen in which the transplant had been covered with periosteum. This may have been due to the fact that the transplant with periosteum was forced into the defect, while the transplant without periosteum was a trifle shorter than the defect. Both transplants seemed in equally good condition.

In 4 other experiments the transplants were without periosteum. In 1 a section of rib 2.2 cm. long, in a radial defect, was still demonstrable after 74 days, but was evidently acting as a scaffold for the formation of bone from the radial fragments, and not from the transplant itself. The radius was shortened. The transplant was of normal thickness in the center of the defect, but was replaced by much thicker bone at its ends. The transplant itself was 1 cm. shorter than when transplanted. The other experiments without periosteum (121, 123 and 126 days) showed disappearance of the transplant in each instance, with shortening and bending of the bone and compensatory thickening of the ulna opposite the defect. There was marked growth of bone from the bone stumps in each instance, which was significant, when compared with the slight growth of bone from the stumps when no bone was placed in the defect.

This group leads us to believe that iso-bone in a bone defect stimulates the growth of bone from the bone stumps; that the bone acts as a sort of scaffold to the growth of new bone, from the living bone stumps; that there is shortening of the bone into which the transplant is placed, and that there is ultimate absorption of the transplant.

#### GROUP XI.

##### MISCELLANEOUS EXPERIMENTS.

The periosteum was removed from the surface of a rib, and on the denuded area two sections of the radius were secured, each being .75 cm. long. One was covered with periosteum; the other was denuded. The wound became infected and the specimen was examined 20 days later. There was marked thickening of the denuded rib, which had been caused by the

irritative action of the infection, and also by the friction of the transplants against it. The X-ray plate showed that the transplant without periosteum was smaller and showed much greater evidence of absorption than the transplant with periosteum. This seems to indicate that the periosteum had had some protective influence against absorption due to infection.

An area of bone from the surface of the femur, 3 x 1 cm. in diameter, was removed down to the marrow cavity, after the periosteum had been stripped from the circumference of the femur in this region. The marrow and endosteum were curetted as thoroughly as possible. The bone strip was scraped and placed on the denuded femur opposite the defect, with the marrow side to the bone, and was held in position by the surrounding soft parts. After 93 days the transplant, much roughened and thickened, was found tightly adherent to the femur. There was also thickening of the femur adjacent to the transplant. The area from which the transplant was taken was marked by a depression which measured 2.7 x .5 cm. in diameter. Along its edges was a rim of new bone. There was also an irregular growth of new bone lining the cavity, but not filling it. Both femurs were of the same length, but the bone which had been operated upon was much thicker and more irregular in appearance. The X-ray plate showed new growth of bone along the femur beneath and beyond the graft, and from the graft itself. The graft showed no sign of absorption and was of the same length as when transplanted.

This shows that auto-bone without periosteum, placed against denuded bone, will live and produce new bone, and will stimulate the bone along which it is placed to produce new bone. In this way a weakened bone might be reinforced. It also shows that there is new growth of bone from the surface of denuded bone, when in contact with denuded bone. This is in marked contrast to the slight overgrowth of bone which occurred when the periosteum alone, or with bone shavings, was removed. There was also growth of bone from the cut surfaces in the shaft of the bone, and also from the surface of the marrow cavity, after a curetting of the marrow and endosteum.

After removal of the periosteum an area of bone, 1 x 1.5 cm., was chiseled out of the shaft of the femur down to the marrow cavity. After 100 days the site of the defect was marked by a depression filled with bone. On cross-section, there was an overgrowth of bone extending into the medullary cavity, probably from the endosteum. This is interesting, as there had been no attempt whatever at overgrowth of bone around the edges of the defect, or from the area denuded of periosteum.

A section of radius, 3.2 cm. long, with its periosteum, was removed, and the periosteum was stripped from the stumps. A celluloid tube was placed around the stumps and so as to fill the defect. After 151 days the celluloid tube was found to be intact. The radius still had a defect 1.6 cm. long. The X-ray plate showed a healing fracture in the ulna at the lowest level of the defect. There was also an irregular, conical outgrowth of bone from each radial stump, which had evidently grown into the celluloid tube. One is struck by the slowness of the growth of bone from the radial stumps



during this length of time; this is very marked when compared with the growth of bone from the radial stumps when either auto- or iso-bone is placed in the defect.

At this time it might be well to remark on the very sluggish growth of new bone from bone stumps, after partial resection of a bone with its periosteum. This was noted in a number of experiments; it is astonishingly slow, being very little more marked after six months than after six weeks.

#### CONCLUSIONS.

Free periosteal transplants did not produce bone in the large majority of experiments, even though osteoblasts were adherent to the transplants.

Pedunculated flaps of periosteum did not produce new bone.

Free periosteal transplants and pedunculated periosteal flaps, with bone shavings attached, produced bone in each experiment. From this we may surmise that bone particles had been accidentally transplanted in those experiments in which bone was found after the transplantation of free periosteum.

The removal of periosteum had little, if any, effect on the nutrition of a bone. The surface from which the periosteum was removed showed very little overgrowth of bone, unless there had been considerable irritation of that surface, either by trauma or by infection. The area from which the periosteum had been taken was covered with a thin, very adherent fibrous membrane; or the muscle tissue was adherent to the denuded area.

Absorption occurred when a silver ring was snugly applied around a bone over the periosteum, and also at times when it was applied around denuded bone. There was no new bone

formed from either the periosteum or bone, when a silver ring was placed around a bone beneath the periosteum.

Both auto- and iso-bone, without periosteum, were effective in repairing skull defects.

Auto- and iso-bone, without periosteum, when transplanted into the periosteal tube after subperiosteal resection of a rib, caused stimulation of bone growth from the periosteum and also from the rib ends.

Transplants, covered with periosteum and also foreign bodies, stimulated bone-growth only from the rib ends.

Transplants of the same size in a periosteal tube, after subperiosteal resection, under exactly the same conditions, acted quite differently.

After subperiosteal resection of a portion of a bone, the growth of bone in repairing the defect was from the bone stumps, the periosteum acting as a limiting membrane.

Auto-bone, both with and without periosteum, lived and was successfully transplanted to fill defects in bone. Clinically, it is advisable to transplant bone covered, in part at least, with periosteum.

Iso-bone in a bone defect acted as a scaffold for the growth of new bone from the living bone stumps, but there was ultimate absorption of the transplant.

Auto-bone, both with and without periosteum, was absorbed when transplanted into soft parts. The periosteum seemed to have some protective influence against early absorption. The fate of those transplants which had grown together and produced new bone is doubtful, but as absorption was going on, and as the tendency of free bone in the soft parts was to be absorbed, it seems probable that absorption would eventually have occurred.

The same may be said of iso-bone in soft parts, except that in no instance was any new bone formed from the transplant.

## THE JONATHAN HUTCHINSON ICONOGRAPHY.

### A PRELIMINARY NOTE.

By WILLIAM OSLER.

I was delighted to hear that through the generosity of Mr. W. A. Marburg, already a liberal donor, The Johns Hopkins Medical School had secured the Jonathan Hutchinson collection of original drawings, colored plates and photographs illustrating clinical medicine and surgery. For a long time I have known the collection, and frequently had the privilege of a demonstration of certain parts by Sir Jonathan himself. In 1900 he gave it as a clinical museum to the Medical Graduate College, and it was my privilege to deliver the opening address on that occasion. The times have been too much for the college, which recently dissolved, and the collection came into the market. I may be permitted to quote a paragraph from that address about Sir Jonathan and his collection:

You have been fortunate in having associated with your college (Medical Graduate College and Polyclinic, England) a man with a truly Hunterian mind. In the broad scope of his work, in the untiring zeal with which he has studied the natural phenomena

of disease, in his love for specimens and collections, Mr. Jonathan Hutchinson bears a strong likeness to the immortal Hunter. No individual contributor in this country has made so many careful observations upon so many diseases. He is the only great generalized specialist which the profession has produced, and his works are a storehouse upon which the surgeon, the physician, the neurologist, the dermatologist and other specialists freely draw. When anything turns up which is anomalous or peculiar, anything upon which the text-books are silent and the systems and cyclopædias are dumb, I tell my students to turn to the volumes of Mr. Hutchinson's *Archives of Surgery*, as, if it is not mentioned in them, it surely is something very much out of the common. It is very fortunate that his collection will be kept together, as it will be of great service to students from all parts of the world. In one respect it is unique, pictorial and clinical, not anatomical and pathological, and it will remain a worthy monument to the zeal and perseverance of a remarkable man, a man who has secured the homage of a larger number of clinical workers than any Englishman of his generation.<sup>1</sup>

<sup>1</sup> The Importance of Post-Graduate Study, *Lancet*, 1900.



The collection consists of:

(1) Original colored drawings, of which there are many hundreds.

(2) Colored plates taken from atlases, books and memoirs.

(3) Engravings, woodcuts, photographs and pencil sketches, very often with the letterpress or manuscript notes attached.

The collection illustrates the whole range of medicine and surgery. Very many of the drawings were specially prepared for the *Atlas of Skin Diseases*, which Sir Jonathan edited for the New Sydenham Society; for the *Atlas of Clinical Medicine and Pathology*, which he edited for the same society; for his *Atlas of Clinical Surgery* and for his well-known *Archives of Surgery*, a copy of which he sent to our library. The drawings are classified; one group, comprising more than 5000, are in large paper envelopes; the other, an even larger number, in large cardboard portfolios. While they illustrate particularly the life work of the collector in syphilis and skin diseases, there is scarcely a department of medicine that has not one or two portfolios devoted to it. It is probably the most remarkable iconography on syphilis ever made; portfolio after portfolio is filled with illustrations on every variety of the lesions of this protean disease. Take at random the labels of some of the rarer items: circumcision chancres, syphilitic herpes, recurrent chancres, vaccination syphilis (a very-fully-dealt-with subject), keloid after syphilis.

The illustrations on skin diseases outnumber the others, and the collection illustrates particularly the rarer forms.

Sir Jonathan was deeply interested in leprosy and in lupus, every possible phase of which is here depicted. Then, many portfolios are devoted to Reynaud's disease, and I see in one portfolio the original drawings illustrating Barlow's paper. Yaws, tattooing, gout, vascular tumors, chloroma, rhinoscleroma, Kaposi's disease, Darier's disease, Bielt's disease, nevus, acromegaly, hermaphroditism (in which portfolio I see the original drawings of Partridge's rare case of double penis) anomalies, deformities—all the odd and peculiar deviations in form and structure are represented. A doctor with a case in any way out of the ordinary would be sure to write to Sir Jonathan, who would at once have a photograph or colored drawing made, so that the iconography represents the experience of his long life.

How may the collection be best utilized? It should first be catalogued, the plates identified, which could easily be done from the well-known atlases and from the works already mentioned. The unpublished colored drawings should be separately indexed. The primary business of a medical student is to get a knowledge of disease, and, if used by teachers, this collection will be of great value in helping them to demonstrate both the common and the rarer types. For the departments of syphilis and of skin diseases it will be invaluable, and there is no reason why the collection should not be distributed where it will be most helpful. In any case, it should be in the hospital side of the medical school library, where the treasures should be made freely accessible to the medical student.

## AN ACCOUNT OF THE SURGERY AND THE SURGEONS OF THE AMERICAN REVOLUTION.<sup>1</sup>

By WALTER B. PLATT, M. D., F. R. C. S. (Eng.).

While thinking over matters connected with the American Revolution it occurred to me that I had very little definite knowledge concerning the medical and surgical work of the army during that war; the men engaged in it, or of their methods. While it is too much to believe that there are many situated as I was in this regard, there may be physicians to whom such facts as I have been able to gather may be in part new. On this supposition I have ventured to prepare this paper.

It was a matter of interest at that time that I could find no work in the library of the Army Medical Museum under the heading "Surgery of the American Revolution," or any similar title. After some inquiry I found several books under other names bearing on this subject. They were those of Dr. Harvey Brown on organization mainly; of Toner, dealing principally with the personnel; of Thacher containing a general sketch of the work of the surgeons, and of Dr. John Jones (1776).<sup>2</sup> I

believe these four works with their references contain the greater part of the material that is available and reliable.

The beginning of the medical department of the American army in the Revolutionary War, and thus of army surgery in this country on an organized basis, was when a large number of citizens of all classes, and among them a number of physicians, assembled at Cambridge, Mass., on the occasion of the siege of Boston, directly after the battle of Lexington, to lend what aid they could. At that time there was nothing in existence to provide for the care of the sick and wounded, and the Second Provincial Congress of Massachusetts, in May, 1775, saw the urgent need of doing something in their behalf.

The first step was taken when they ordered "That the President *pro tem.*, with Drs. Church, Taylor, Holten and Dunsmore, be appointed a committee to examine such persons who are or who may be recommended as surgeons for the army

Thacher's Military Journal during the Revolutionary War, from 1775 to 1783. Second Ed., Boston, 1827.

Plain and concise practical remarks on the treatment of wounds and fractures, to which is added an appendix on camp and military hospitals; principally designed for the use of young military and naval surgeons in North America. By Dr. John Jones. Philadelphia, 1776.

<sup>1</sup> Read before The Johns Hopkins Historical Club.

<sup>2</sup> Historical Notes concerning the Medical Department of the United States Army. By Harvey W. Brown, Assistant Surgeon U. S. A. 1873.

Medical Men of the Revolution. By Dr. John M. Toner, Philadelphia, 1876.



now forming in the Colony," and "*Resolved*: That persons recommended by commanding officers of the several regiments be appointed surgeons of their several regiments provided they appear duly qualified upon examination." Drs. Whiting, Bayliss, Hall, and Jones were added to this committee not long afterward. We learn from Thacher's "*Military Journal during the American Revolutionary War*" that sixteen applied the first day and that ten of these were accepted.

The first military hospital of the war was established directly after the battle of Bunker Hill in a number of private houses, and the man in charge was Dr. John Warren, the brother of Dr. Joseph Warren who commanded the troops on that occasion. It may be well to state at this time that the words "hospital service," as used in Acts of Congress and formal communications, usually meant medical bureau or department, and not simply a hospital in the ordinary acceptation of the word. Soon after Dr. Isaac Foster, of Cambridge, succeeded Dr. Warren, and was made Deputy Director-General; and other hospitals were established at Roxbury and Watertown, besides a fourth for smallpox cases.

The organization was upon a simple plan. Each hospital had two surgeons and two surgeon's mates, while each regiment had one surgeon and two surgeon's mates. Colonels of the regiments had the nomination of the surgeons, and the surgeons might nominate their mates.

The pay of the hospital surgeons was fixed at eight pounds per month, and that of the mates at four pounds ten shillings per month.

As might be imagined, the plan of nomination by the colonels did not improve the efficiency of the surgeons, although a number of very genial fellows were doubtless brought to the front by this system. The lack of efficiency was so manifest that Congress speedily overhauled the medical department, and Gen. Washington, who saw the extreme importance of maintaining the highest excellence in this branch of the army, sent a message to the president of Congress in which he said that there was lack of discipline among the surgeons, that disputes and contentions abounded, and that he would like to have the department put under proper regulations. This spirit of contention, indeed, was the chief bane of the army and hospital surgeons from the beginning to the end of the war, and seemed to be the habit of the time in the profession the world over. I believe this was due less to the character of the physicians than to the condition of medicine at that time, in which there was too much metaphysics and too little physics, and because men were trying to deal with purely physical conditions on a metaphysical basis. Physicians had little that was real to stand upon, apart from the splendid achievements of anatomy, and their foundations in medicine were frequently thrown down because built upon speculation instead of fact; the essence of disease was regarded a matter to be settled by argument, and its treatment was reasoned out in the study instead of in the laboratory or by the bedside. Consequently they argued and disputed, and not being convinced, fought with wordy weapons.

Dr. Benjamin Church, the first head of the hospital department of the army, was a man of great ability, dignity and magnetism, apparently an ardent patriot, and certainly a fine

orator. After his appointment, however, he was an uncommon failure from every standpoint. He turned out to be quarrelsome, complaining, and negligent; and worst of all, was finally detected in sending secret messages to the British by the hand of a woman. For this, a crime deserving death, he suffered a long imprisonment. Being finally allowed to leave the country, he sailed for the West Indies on a ship which was lost at sea.

His successor in office was likewise a man of great ability, ripe culture, and considerable experience; for, Dr. John Morgan of Philadelphia was a remarkable man. He had been a pupil of John Hunter and returning to America had united with Shippen and the Bonds in founding a medical school. His previous military experience as a surgeon had been acquired in the French and Indian War. On taking charge, he found the hospitals full of cases which ought to have been cared for in the field. He cleaned up the service as well as the hospitals, sending back many surgeons to the field, and soldiers, who were able to fight, to the front. A number of surgeons unqualified for the work he discharged and made every effort to improve the service.

In December, 1775, Congress raised the pay of surgeons to \$25 per month and of surgeon's mates to \$18.<sup>3</sup> The campaign against Quebec was not the conspicuous success it had been in the French and Indian War; the army found itself short of hospital supplies, with an abundance of cases of smallpox and nostalgia on hand; two diseases we hear more of in the early days of our country than at the present time. However, the health of the troops about Cambridge continued good during the summer of 1775, until the arrival of troops from the Middle and Southern States, when dysentery, typhus and typhoid began to claim many victims. The seat of war was now transferred further south with headquarters at New York, and the hospitals, which had been merely receptacles for the sick, with little to make them habitable, had plenty of supplies.

Morgan would have made a capital hospital superintendent, for his great talent was again shown in cleaning out the hospitals, and reducing the number of inmates in his district to eighty. Once more there was friction between the army surgeons and the hospital surgeons, the former thinking that the latter had an easy berth with plenty of supplies, which they withheld from those in the field. Only army rations were given to the sick, and of course these were entirely unfit for men suffering with suppurative fever and dysentery.

In the summer of 1776, almost at the outset of the war, there was again a dearth of hospital supplies, about which Dr. Stringer made complaint to Gen. Gates. The limits of authority of the different medical officers were so ill-defined, that friction could not fail to take place constantly, and much of the time which could have been better employed was taken up with complaints of each other. Dr. Stringer went directly to Congress to complain of Dr. Morgan, the final result being the dismissal of both from the service. The surgeons certainly should not have been held responsible for the scarcity of hospital supplies. We learn that the supply of bandages at this time was not sufficient for fifty men; there was no straw for bedding for the sick, and the army was on the verge of mutiny.

<sup>3</sup> This probably refers to the field, not to the hospital, surgeons.



Gen. Gates wrote that the neglect was shameful, and Gen. Greene complained bitterly of the treatment of his soldiers because of the incompetence of the surgeons.

As far as Dr. Morgan is concerned, he seems to have done what he could, and although finally vindicated by Congress, he died of a broken heart by reason of the injustice done him. Dr. Benjamin Rush, the father of American medicine, says he was respected by the officers and beloved by the soldiers, and that "he had an uncommon capacity for acquiring knowledge, a memory extensive and accurate, and was intimately acquainted with the Latin and Greek classics. He had read much in medicine, and in all his pursuits he was indefatigable and persevering. He evinced an amiable and exemplary tenderness toward the sick." His failures, Dr. Rush believed, were due to causes beyond his control.

Dr. Shippen devised a plan of organization taken from that of the British Army and better than the one then in existence, but too complex for American use at that time. It received the commendation of Gen. Washington. It was as follows:

Dr. Wm. Shippen, Jr., was chosen, by unanimous ballot of the thirteen States, Director-General of all the military hospitals for the armies of the United States.

Dr. Walter Jones, Physician-General of the Hospital in the Middle Department.

Dr. Bénj. Rush, Surgeon-General of the Hospital in the Middle Department.

Dr. John Cochran, Physician and Surgeon-General of the Army in the Middle Department.

Dr. Isaac Foster, Deputy Director-General of the Hospital in the Eastern Department.

Dr. Ammi Ruhamah Cutter, Physician-General of the Hospital in the Eastern Department.

Dr. Philip Turner, Surgeon-General of the Hospital in the Eastern Department.

Dr. William Burnet, Physician and Surgeon-General of the army in the Eastern Department.

Dr. Jonathan Potts, Deputy Director-General of the Hospital in the Northern Department.

Dr. Malachi Treat, Physician-General, in the same.

Dr. Forgue, Surgeon-General, in the same.

Dr. John Bartlett, Physician and Surgeon-General of the army of the Northern Department.

Washington always recognized the importance of the surgical service of the army and recommended a liberal compensation to surgeons. In a letter to John Hancock dated March 14, 1777, he writes, "There is one thing which claims in my opinion the earliest attention of Congress, I mean the pay of regimental surgeons and that of their mates. Those appointments are so essential that they cannot be done without. Their pay in the first instance, is so low, so inadequate to the services which should be performed, that no man sustaining the character of a gentleman and who has the least ability and skill in the profession can think of accepting it; that of the latter is so mean that no one of the least generosity, sentiment or pretensions to merit can consent to act for it. In a word these are inconveniences of an interesting nature; they amount to an

exclusion of those persons who could perform the duties of those offices, and if not redressed, there is not the smallest probability that any can be prevailed upon to enter them again." Whatever criticism we may make upon Gen. Washington's English, we cannot say that his meaning is ever obscure.

That Washington took a continued interest in the personnel and morale of his surgeons is shown by a letter to Hancock where he writes, "No less attention should be paid to the choice of surgeons than of other officers of the army. They should undergo a regular examination, and if not appointed by the Director-General and surgeons of the hospital, they ought to be subordinate to and governed by his directions. The regimental surgeons I am speaking of, many of whom are very great rascals, countenancing the men in sham complaints to exempt them from duty, and often receiving bribes to certify indispositions with a view to procure discharges or furloughs. In short there is a continual bickering among them, which tends greatly to the injury of the sick, and will always subsist until the regimental surgeons are made to look up to the Director-General of the hospital as a superior. . . . The regimental surgeons are aiming, I am persuaded, to break up the general hospitals, and have in numberless instances drawn for medicines, stores, etc., in the most profuse and extravagant manner for private purposes."

That the regimental surgeons were not the only ones who received hard words, and that officers were not of one mind in this matter, the following letter of Gen. Smallwood of Maryland to the Council of Safety of his state will show. He says, "The Directors of the general hospitals who supply and provide for the sick, are extremely remiss and inattentive to the well-being and comfort of these unhappy men; out of this train they cannot be taken. I have withdrawn all mine long ago and placed in comfortable houses in the country and supplied with only the common rations. Even this is preferable to the fare of a general hospital. . . . One good-seasoned and well-trained soldier recovered to health is worth a dozen new recruits, and is often easier recovered than to get a new recruit, exclusive of which, this neglect is very discouraging to the soldiery, and must injure the service on new enlistments after the troops go into winter quarters." That the devotees of Mars have always offered oblations to Venus even in the hardest times, the following resolution passed by a committee of Congress in 1778 while the army was stationed at Valley Forge will show: "*Resolved*, That the sum of ten dollars shall be paid by every officer and the sum of four dollars by every soldier, who shall enter or be sent to any hospital to be cured of a venereal disease, which sum shall be deducted out of their pay. . . . The money so arising to be paid to the Director-General or his order, to be appropriated to the purchasing of blankets and shirts for the use of sick soldiers in the hospital." There is no evidence that there was any result from this resolution one way or the other, either in diminishing the number of such cases, or in producing a considerable revenue in consequence of this drastic measure.

Thacher gives us the following picture of an American hospital during the Revolution. This one was at Albany, and the



time just after Burgoyne's surrender. "This hospital is now crowded with officers and soldiers from the field of battle; those belonging to the British and Hessian troops are accommodated in the same hospital with our own men, and receive equal care and attention. The foreigners are under the care and management of their own surgeons. I have been present at some of their capital operations, and remarked that the English surgeons perform with skill and dexterity; but the Germans, with a few exceptions, do no credit to their profession. Some of them are the most uncouth and clumsy operators I ever witnessed, and appear to be destitute of all sympathy and tenderness towards the suffering patient. Not less than one thousand wounded and sick are now in this city. The Dutch church and several private houses are occupied as hospitals. We have about thirty surgeons and mates, and all are constantly employed."

Exactly what the methods were of operating, and dressing wounds during this war I have not been able to determine. I have not found any accurate and full account of this matter, and do not believe that careful records of operations and of wounds were kept by any one. It is safe to conclude that their methods were at least as good as those of any army of that day, considering the means at their disposal. Apart from anaesthesia, fewer advances had been made in military surgery from the time of the American Revolution to our own war between the states, beginning in 1861, than in other branches of medicine. In neither war were gauze dressings used, nor was there any idea of aseptic or antiseptic surgery. In both wars, much supuration was taken as a matter of course. In both it is fair to believe that septicæmia and suppurative fever abounded. Certainly in our late Civil War hospital-gangrene occurred, and maggots infesting wounds were seen not infrequently. From the fact that round bullets were exclusively used in the Revolutionary War, it is certain that gunshot wounds were of a somewhat different character from most of those in our Civil War, and it is probable that sabre and bayonet wounds were relatively more common than in our Civil War. In both wars it was observed that wounded soldiers did much the best who were gotten into hospital tents, and out of houses, and that buildings with high roofs were far better for the patients than the best of ordinary houses. It is safe to believe that tetanus was about as frequent in one as in the other.

Here are the names of some of the physicians, surgeon-generals and deputies of the different departments from 1776 to 1783 in the Army of the American Revolution:

John Morgan (Pa.).	Philip Turner (Conn.).
John Warren (Mass.).	Jas. Tilton (Del.).
Isaac Foster (Mass.).	Malachi Treat (N. Y.).
Benj. Rush (Pa.).	Moses Bloomfield (N. J.).
John Cochran (Pa.).	Thomas Bond (Pa.).
Jas. Craik (Md.).	James Brown (Md.).
William Eustis (Mass.).	Wm. Brown (Md.).
Dr. Wm. Shippen (Pa.).	Jonathan Potts (Pa.).
Walter Jones (Va.).	Dr. Forgue (Conn.).
Samuel Stringer (Md.).	Dr. Charles McKnight (N. J.).
Wm. Rickman (Va.).	Dr. Wm. Burnett (N. J.).
Ammi R. Cutter (N. H.).	

There were twenty-three who were either surgeon-generals or deputies. There were altogether twelve hundred men in the surgical service of the army. A large number of these had already had some experience in military surgery during the French and Indian War, while nearly all of the men at the heads of departments had had exceptional opportunities in European hospitals, and schools of medicine.

I will give some details concerning a few of the most prominent men.

Dr. William Shippen, Jr., born in 1736 and died 1808, at the age of 72 years. He graduated at Princeton in 1754 and at Edinburgh in 1761; had previously studied medicine with his father and later with the two Hunters, Wm. Hewson, Sir John Pringle, Cullen and the elder Munroe. He taught anatomy at the College of Philadelphia Medical School and was made chief physician for the Flying Camp in July, 1776. On April 11, 1777, he was made director-general of all the hospitals in the army. In 1798, his only son died, after which he seemed to lose all interest in his profession and in his medical school, and resigned his commission in June, 1781. Another account says that in 1776 he was made medical director at Trenton, and that later he had entire supervision of all camps on the west bank of the Hudson River.

Samuel Stringer was a native of Maryland. He studied medicine with Dr. Bond of Philadelphia, and served as surgeon throughout the French and Indian War in the British Army. He was made director-general of hospitals August 20, 1776. Was discharged January 9, 1777, and died at the age of 83 years.

John Morgan, M. D., F. R. S., was born in Philadelphia in 1735. He was educated in Maryland, graduated in Philadelphia in 1754, and studied medicine with a Dr. Redman in that city. He served as surgeon in the French and Indian War. In 1760 he went to France, and later attended lectures and dissections by Wm. Hunter, graduating at Edinburgh in 1763. He studied under both the Munroes, Cullen, Rutherford, Hope and others. He knew Voltaire and Morgagni. He was made an F. R. S. in London, and was appointed professor of theory and practice in the Medical College of Philadelphia. He died in 1789 at the age of only 54 years. The cause of his death was grief and disappointment at the injustice done him by his dismissal from the army. A sketch of his work has already been given.

Dr. William Rickman was made physician and director-general of hospitals in Virginia, later director-general of hospitals in the Southern Department. He was charged with neglecting to care for his patients from Virginia and North Carolina at Alexandria, but the charges were dismissed.

Benjamin Rush, perhaps the most prominent of all our early American physicians, was born in 1745, and was graduated at Princeton, in 1760. He took his M. D. in Edinburgh in 1768, practised in the London and Paris hospitals, and returning to America, was made professor of chemistry in the Medical school in Philadelphia. From the first he was a great patriot and represented Pennsylvania in Congress (Colonial) in 1776. He is well known as one of the signers of the Declara-



tion of Independence. He was widely known, not only as a physician but as a public-spirited man and a citizen. He was not fond of surgery, but accepted the position of physician-general to the army. He received but little lustre from his military career, and was constantly complaining to Congress about his superiors. It is said that Gen. Washington thought he had written anonymous letters and he was suspected of a connection with the wretched Conway cabal (1777). However this may be, Washington made him director of the Mint, and he held this position for fourteen years. (See American Revolution, by Fiske.) He was one of the founders of Dickinson College. In 1811 the Emperor of Russia sent him a gold ring as a testimonial of appreciation of his professional ability. He died April 14, 1813, at the age of 68 years.

Philip Turner was born in Norwich, Conn., in 1740, and was one of the few of the prominent men of his group whose studies were carried on in this country exclusively. He served in the French and Indian War as assistant surgeon to a Provincial regiment at Ticonderoga. Returning in 1783 to Norwich, he married his preceptor's daughter. He soon gained a reputation as a skillful operative surgeon. He was the first surgeon of Connecticut troops at the siege of Boston, and is said to have been the most skillful operator in the Army of the Revolution. Dr. Shippen remarked that he had never seen any one who excelled him as an operator, in Europe or America. He was successful in 18 out of 20 lithotomies, a large percent in those days, and a good one in any generation. His fame, rather than any influence, gained him the position of director-general in the reorganization of the medical department of the army. From motives of policy it was deemed best to reconsider the vote, and Dr. Shippen was then given the position.

William Burnett graduated in 1745 at the College of New Jersey, then located at Newark. He seems to have been a gentleman of culture.

Dr. Walter Jones of Northampton County, Virginia, appears to have been a man of parts. He graduated at Edinburgh in 1769-1770, and was made physician-general of the army. He found the office little to his taste, for he resigned after holding the position two months and returned to his private practice. He was a graduate of St. Mary's College, Virginia, in 1760.

Charles McKnight was a native of New Jersey, born October 10, 1750. He was graduated at Princeton, in 1771, pursued his studies with Dr. Shippen, and was appointed senior surgeon of the Flying Hospital of the Middle Department. At the end of the war he went to New York City to reside, where he had the distinction of being one of the first physicians in New York to use a carriage. He was professor of anatomy in Columbia College, and published a successful result of an operation for extra-uterine pregnancy.

Ammi Cutter was a native of Maine, born 1730, and died 1819, aged 89 years. He was graduated from Harvard College in 1752, and served during the French and Indian War in 1758. He was also given the honorary degree of M.D. by Harvard College.

Dr. William Brown, of Maryland, was the successor of Benj. Rush. He graduated at Edinburgh, in 1768. His private practice and home were in Alexandria, Va. The physicians of Maryland in Revolutionary days, like some of their successors of to-day, were fond of politics. In the former days they were generally looked to for advice in the Councils of Safety, and among these we find the names of Dr. John Archer of Harford County, of Ephraim Howard of Anne Arundel County and of Richard Brooks of Prince George County.

In the list of these men, there are one or two more points of especial interest. At the time of his death Dr. Rush was 68 years of age. Dr. Shippen 72 years of age. Dr. Cutter 89 years of age. Dr. Turner, 75 years of age. Dr. Stringer, 83 years of age. Dr. Morgan, 58 years of age.

Concerning their early education, Drs. Shippen, Rush, Jones, McKnight, Cutter and Morgan had both academic and medical degrees. Dr. Burnett had only an academic degree and Dr. Turner, one of the best of them all, had neither.

It is clear that with the experience they had gained in the French and Indian War these men were most valuable to direct the medical department of the army, and also it is obvious that an army, which was short of clothing and shoes at times, could not be expected to have at all times an abundance of medical supplies. Our greatest regret is that more complete records and details of their work have not been left behind, for plenty of work was done and most of it under great disadvantages.

## PROCEEDINGS OF SOCIETIES.

### THE JOHNS HOPKINS HOSPITAL MEDICAL SOCIETY.

JANUARY 4, 1915.

#### Exhibition of Case. DR. F. A. EVANS.

This patient, Dr. A., has been practising medicine in Fayoum, Egypt, for the last 15 years. He entered the hospital on Dec. 23, 1914, complaining of cysticercus cellulosa cerebri. His family and personal history has no relation to his present illness. The present illness began in March, 1912, when he first noticed segments of tapeworm in his stools. He was able to recover the worm, but could not find the head. In May, 1913, 13 months later, he again noticed segments, but was unable to find the head. He had a severe convulsion at this time, with no premonitory symptoms except an intense nausea for about 30 seconds before

the onset. He says he was unconscious for 30 minutes. The attack was followed by severe subconjunctival hæmorrhage and injection of the eyeball. Two months later, July 1913, 15 months after he had found the first segments in his stools, he noticed what he diagnosed as cysticerci in the subcutaneous tissue. These were most abundant in the temporal and masseter regions and on the forearms. For a period of six months they occurred in successive groups. In Nov., 1913, one was removed with the result that the patient's diagnosis was confirmed by Drs. Toors and Ferguson of Kasi el Ainy and his case presented before the Cairo Medical Society. In the previous July he had gone to Austria and during the voyage was very seasick. Dr. A. himself suggests the hypothesis that during the attack he had regurgitated some of the segments and infected himself. In Jan., 1914,



he had a second severe convulsion, similar to the first. From that time until May, 1914, he was practically free. Between May and Nov. 5, he had the third, fourth, fifth and sixth convulsions. The third and fourth occurred without premonitory symptoms. The fifth and sixth were only 12 days apart and each was preceded by a twitching of the right arm. For four or five days preceding the fifth general convulsion he had noticed difficulty in writing and a tendency to drop the second and fourth letters in his signature. Before the sixth there was simply the premonitory twitching of the right arm. On Nov. 28 and continuing until Dec. 16, he had a series of what he describes as epileptiform seizures of the left arm, lasting for five or ten minutes and quite severe. On one or two occasions the left foot was involved and once he almost fell. For the last year and a half he has been troubled with numerous headaches of sudden onset and as sudden disappearance, associated with visual error and inability to pick up the next line in reading. At no time have ova been found in his stools, and the stools of his family and servants have also been examined with negative results. He has eaten very little pork, and never, so far as he is aware, except when it was well cooked. The parasite, however, was the *tænia solium*.

Physical examination showed a sparely nourished, afebrile man, slightly pale. The uvula was retracted slightly to the right on phonation. The thyroid isthmus could be palpated, but no eye signs and no visual disturbances were noted. In fact there was no evidence of involvement of any cranial nerves. In the posterior cervical region, there was a small nodule about the size of a pea, but Dr. A. does not believe that this is a cyst. There was some arteriosclerosis and a slightly enlarged liver. R. b. c. 4,967,000; w. b. c. 6,960; hæmoglobin 94 per cent. The differential count showed 35 per cent neutrophiles, 3 per cent eosinophiles, 1 basophile only in 300 cells, 45 per cent small mononuclears, 11 per cent large mononuclears and 2 per cent transitionals. There was no abnormality of the red blood cells. Repeated examinations of the stools were negative for parasitic ova. The Wassermann was negative. The eye-grounds were normal. Repeated examinations of the urine revealed no pathological condition; there was no sugar. On X-ray examination of the head, Dr. Waters described a small shadow in the pineal region, showing three small dense areas and tapering off in the direction of the sella, suggesting a tad-pole appearance. Calcification of the pineal gland and of the choroid must be considered, but the shadow is not typical of these conditions, and Dr. Waters, taking his findings in conjunction with the history, favors the diagnosis of *cysticercus cerebri*.

#### Anti-typhoid Vaccination. MAJOR E. R. WHITMORE, U. S. A.

Major Whitmore described the vaccine used by the United States Army and the technique employed in its preparation. The vaccine is derived from a single strain of low virulence obtained from a patient at Netley, England, in 1900.

In discussing the length of time that the vaccine retains its immunizing qualities, Major Whitmore spoke of the results obtained by Leishman, who sent a supply of vaccine to India which was not kept in a refrigerator. It was tested after six months and found to be still good. The United States Army, however, insists upon a time limit of four months.

The administration calls for subcutaneous injection, which is followed by a local and sometimes by a general reaction. Russell kept a record of over 130,000 injections and found that in over 96 per cent the general reaction was mild or absent.

Vaccine treatment was inaugurated in the army in 1909, and in 1911 vaccination was made compulsory for all persons mobilized in the camp in Texas. There were 13,000 men in camp for a period of four months, with only two deaths from typhoid, a decided contrast to conditions in the camp of 11,000 men in Jacksonville during the Spanish-American War, where, with

similar surroundings, there were 2693 certain or probable cases of typhoid, with 214 deaths from the disease. There have been no cases of typhoid in an army camp since 1911. In September, 1911, vaccination was made compulsory for all persons under 45 years of age. During the past year there were six cases of typhoid in the whole army, two in unvaccinated men and four in vaccinated men. Of these latter, three had received one dose and one had received a second dose of the vaccine just before entering the hospital. It is evident, therefore, that all four patients had been infected before receiving the vaccine.

The duration of the immunity seems to be uncertain. In some patients agglutination disappeared from the blood within two years. In the army, the dosage for a second administration of the vaccine is the same as that given the first time.

In regard to the question of the negative phase—as to whether vaccination increases susceptibility for a time—statistics compiled by various observers fail to show any proof in favor of this theory, especially when the present mode of vaccination is employed.

With regard to the contention that tuberculosis is caused by the vaccine, statistics show that tuberculosis is actually decreasing in the army and also in the navy, where vaccination is also compulsory.

Vaccination for typhoid is of course now quite common, but one is not ready yet to advise it for the general community. To persons, however, who intend to move into a locality where typhoid fever is prevalent and to travelers, who cannot be sure what they are eating or drinking, this prophylactic measure would seem to be a wise precaution.

#### Diphtheria Bacillus Carriers. DR. C. G. GUTHRIE.

This communication referred to work carried on by Dr. Guthrie, Dr. Moss and others, which will be reported in detail later. The incidence of the diphtheria bacillus carriers was determined by the study of over 6,000 throat cultures. Continued study showed a striking discrepancy between the number of carriers and the instances of clinical diphtheria. Whenever positive cultures were encountered, the diphtheria organisms were isolated and the original findings confirmed by careful study. It was found that from 80 to 90 per cent of the carriers harbored organisms which were avirulent. These organisms were typical both morphologically and culturally, and differed from the virulent organisms only in their inability to produce toxin. The validity of the guinea-pig test for virulence was confirmed by throat inoculations in human volunteers. The avirulent organisms caused no lesions, whereas the ones, that had previously been determined to be virulent by guinea-pig inoculation produced clinical diphtheria. As a result of the human inoculations, some of the volunteers became carriers and were carefully followed for months, or until they became free from diphtheria bacilli. Isolations were made from their throats at frequent intervals and it was found that the organisms retained their original characteristics—that is, the virulent organisms remained virulent, while those originally avirulent continued so after many months' sojourn in the human throat. As a result of this study, it is believed that carriers of avirulent diphtheria bacilli constitute no menace to the public health.

JANUARY 18, 1915.

1. \* Studies on the Relation Between Diet and Pellagra. DR. CARL VOEGTLIN.
2. \* A Brief Review of Some Phases of the Work of the Robert M. Thompson Pellagra Commission. DR. J. V. SILER.

\* These papers, together with the discussions, will appear later in the BULLETIN.



## THE JOHNS HOPKINS HOSPITAL HISTORICAL CLUB.

JANUARY 11, 1915.

1. \* Mithridatium and Theriac. The Most Famous Remedies of Old Medicine. DR. GEORGE W. CORNER.
2. \* Dr. John W. Francis: Medical Editor and Writer. DR. C. W. G. ROHRER.

## THE LAENNEC.

JANUARY 25, 1915.

1. \* The Relation Between Clinical and Laboratory Data in Tuberculosis. DR. A. H. CAULFIELD.
2. \* Some Cultural Studies on the Tubercle Bacillus. MR. S. A. PETROFF.

## NOTES ON NEW BOOKS.

*A Treatise on Clinical Medicine.* By WILLIAM HANNA THOMSON, M. D., LL. D. Cloth, \$5. (Philadelphia and London: W. B. Saunders Company, 1914.)

In his preface the author states that a treatise on clinical medicine should chiefly consider those subjects which concern the physician in dealing with the living patient. As a suitable introduction to such a treatise he devotes a section of some 60 pages to a discussion of common symptoms, the proper interpretation of which are of vital importance. These symptoms are "catching cold," pain, emaciation, cough, dyspnea, edema and vomiting. The treatment of some of these is good, of most, valueless. He divides remedies into non-medicinal and medicinal, including in the first group "electricity, cold, heat and change"; medicines being of two kinds, functional and constitutional. This latter classification is hardly in accord with modern pharmacological views.

Part 2 is devoted to the infections, which are classified according to their usual mode of communication. Here there are some rather glaring inconsistencies. Typhoid fever is not included in the group of acute infections which are directly contagious, while under chronic infections, which are directly contagious, are included tabes, paresis and gonorrhea. Acute poliomyelitis is not included under infections at all and the sporadic form is "due to cold affecting some branches of the interior spinal area."

The main portion of the book is taken up with the diseases of the special tissues and organs. The chapter on diseases of the blood is an excellent example of the method employed. Thus, pernicious anemia is treated in less than two pages and is characterized by "specific red cell changes, especially by their increased size so that they are called megaloblasts." No mention is made of what happens to the leucocytes. Four lines suffice to cover the treatment of leukemia and benzol is not mentioned. Paroxysmal hemoglobinuria is treated "by the use of warm instead of cold water." One page covers all the diseases of the spleen. No mention is made of the value of the modern tests for renal function and believing that most of the conditions of chronic nephritis are due to infections by *B. coli*, the author recommends careful treatment of the intestinal digestion: he also gives ten-drop doses four times a day, continuously, of tincture of aconite and 1/24 gr. of corrosive sublimate three times a day. Indicanuria is said to be a morbid condition of the urine which should be treated with urotropin. Bence-Jones' proteinuria receives no notice.

The treatment of diabetes "must be wholly empirical." Codein, cod liver oil, iron and Pluto water are recommended in obvious preference to an intelligent study of the patient's dietetic possibilities. Similarly, since "clinical facts furnish much more trustworthy information than any chemical theories about the nature of gout," the author utterly disregards the value of dietetic treatment and relies upon colchicum and Laville's extract. Exclusive of goiter and exophthalmos, the author cites no less than 27 other "distinctly characteristic symptoms of Graves' disease," included in which are vertigo, itching, vesical irritability and sudden death from syncope. The lead line due to "sulphite of lead should always be looked after, as it may be removed by a daily use of the tooth brush." Migraine is regarded as essentially a digestive disorder.

Albuminuric retinitis is included under disorders of the cranial nerves. Similar glaring inaccuracies could be quoted almost *ad infinitum*. Mention of the Wassermann reaction is nowhere to be found.

The book is not illustrated and is poorly indexed.

*The Ileo-Cæcal Valve.* By A. H. RUTHERFORD, M. D. (Edin.). 70 pp., with 2 colored and 20 black and white plates. \$2.25. (New York: Paul B. Hoeber.)

Neither the importance of the subject nor its treatment justifies the presentation of this thesis in book form. Almost one-third of the book is consumed in individual protocols of numerous specimens. The photographs are as redundant as the text, and add but little to its elucidation. The amount of original research represented is scanty, and the summary adds nothing to our present conceptions of the anatomy and physiology of the ileo-cæcal valve.

*The Pharmacy Handbook.* By F. W. CROSSLEY-HOLLAND, F. C. S., Pharmacist, Member of the Pharmaceutical Society of Great Britain, etc. (London: Henry Frowde and Hodder & Stoughton, 1914.)

The title is misleading, inasmuch as the book does not deal with the pharmaceutical art, neither does it include subject matter that is found in the various treatises on pharmacy. However, as a book of reference, it contains valuable information gleaned from various sources and conveniently arranged. The treatment of such subjects as serums, colloids, anæsthetics and pharmaceutical bacteriology are thoroughly up to date and should be found very helpful to the pharmacist and physician.

*A Text-Book of Medical Diagnosis.* By JAMES M. ANDERS and L. NAPOLEON BOSTON. 1248 pp. (W. P. Saunders Co., 1914.)

This volume is the second edition to appear within three years, and according to the statement of the editors the process of revision of the first edition has been going on for the past two years.

The aims of the book have been first, to furnish an improved method of determining the clinical features of disease, and second, to emphasize the importance of correlating symptoms with the structural changes which cause them.

After a short introduction which covers general and special considerations in the investigation, history-taking and physical examination of the patient, the diseases of the various systems of the body are taken up. These include disorders of the respiratory systems, circulatory, digestive, urinary systems, acute infectious diseases, animal parasitic diseases and constitutional diseases. A special section is devoted to diseases of the nervous system. The various subheadings under these systems are treated according to the following scheme: pathological definition of the condition, the exciting and predisposing factors, the physical complaint and symptoms, the physical signs, laboratory diagnosis, summary of the diagnostic features, and finally differential diagnosis of the condition. No treatment is given. Throughout the book there are a number of differential tables which should prove quite helpful.



It is rather curious that this second edition, which contains a discussion of the electro-cardiogram, the cobra venom reaction in syphilis and other newer diagnostic aids, should make no mention of the modern and widely accepted tests for renal function; nor is there any discussion given of the examination of the cerebro-spinal fluid.

Among the features to be criticized, a few will be mentioned. Under parasitic diseases of the skin, no reference is made to infections with pediculi. The recent studies on the significance of the Bence-Jones body have been overlooked, and the test given for its detection is of no value. The reagent advised for use in the Esbach method of quantitative albumin estimations has long since been discarded in favor of the more satisfactory Tsuchiya's reagent. Under typhoid fever the statement is made that the Widal reaction is usually obtained at the end of the first week and it is given obvious preference as a diagnostic measure over blood cultures. It is hard to understand just why Addison's disease is included under abnormal conditions of the urinary system. Similarly, it seems rather inconsistent to classify exophthalmic goiter, acromegaly, arthritis deformans and Paget's disease under diseases of the central nervous system.

A great many illustrations are scattered through the text, the majority of which are perhaps useful. The colored plates are fair.

It is a grave question in the mind of the reviewer whether such books are really to be commended. The endeavor to incorporate within one volume so much information, about so many different conditions, must of necessity lead to a brevity of description that tends to the development of a similar short-sightedness on the part of the person using the book. It leaves entirely too much to the imagination, in many instances, to make the book of true value to the beginner. To the seasoned practitioner the volume doubtless will prove of considerable aid as a quick and ready reference. But it is possible that even here it will not fully satisfy the mind which is genuinely intent upon learning once and for all the essential clinical and laboratory features which make for sure and intelligent diagnosis. S. R. M.

*Diseases of the Heart.* By JOHN COWAN, D. Sc., M. D., F. R. F. P. S. (Philadelphia: Lea & Febiger, 1914.)

New books, like new acquaintances, are bound to give the reader a new viewpoint, and will question the validity of his own conceptions. Especially is this true if the author has had the extensive experience of John Cowan—the descendant of the long line of well-known Scottish physicians. His recently edited book of 450 pages sums up his clinical opinions, and, with the assistance of very short chapters by Arthur Ballantyne on the ocular manifestations in arteriosclerosis, and by W. T. Ritchie on the electro-cardiogram, endeavors "to review the whole subject (of cardiac knowledge) in the light of recent advances."

The whole could well be divided into four parts, of which physiology, pathology, physical signs and symptoms, and treatment, are section headlines. The author illustrates abundantly with tracings and case histories, obtained, for the most part, in his own clinic. His conclusions may sometimes be questioned, especially as in his interpretation of polygraph curves he writes, in discussing the apex cardiogram: "with relaxation of the ventricle, the curve rapidly falls, and as soon as the pressure within the auricle exceeds the pressure within the ventricle, the auricular-ventricular valves open—a time which coincides fairly accurately with the lowest point upon the tracing. Succeeding the fall there is often a well-marked wave—an instrumental fault due to the momentum of the recording lever and best marked in cases where the fall is most abrupt." This interpretation of rather fundamental points—the protodiastolic wave and the opening of the auricular-ventricular valves—is certainly not gener-

ally acceptable, and would seem to have been proved wrong by the work of Henderson, Thayer, and others.

The discussion of the types of coupled rhythm is interesting and suggestive. His deductions, based as they generally are on polygraphic tracing without the electro-cardiographic findings, are debatable in many instances, and especially in regard to his diagnosis of nodal extra-systoles. In view of his effort to portray the recent advances, it is surprising that only a small paragraph in the section of the pathology of acute endocarditis is granted the streptococcus viridans and its manifestations.

The book, while in no way the reference book of Hirschfelder or Lewis, nor a book to be put in the hands of untrained medical students, is very valuable, and can be profitably studied by the medical profession. In reading it the general practitioner can hardly fail to appreciate the importance of the use of polygraphs for the exact study of his cardiac cases.

*A Reference Handbook of the Medical Sciences.* Vol. IV. By various writers. Third edition edited by THOMAS LATHROP STEDMAN, A. M., M. D., EMB-HAY. Cloth, \$7. (New York: William Wood & Co., 1914.)

This volume, like its predecessors, is attractively bound, well printed, and contains a large number of excellent illustrations. The articles are wide enough in scope to cover the needs of the general practitioner. The subjects of diseases of the foot, fractures, gunshot wounds, etc., have been handled in such a way as to furnish very definite and helpful guides both to diagnosis and treatment. The article on "Foods for the Sick" takes due recognition of protein, fat and carbohydrate contents, as well as of the caloric value of food materials, and shows how such figures may easily be applied to very great advantage by the practitioner.

An interesting article, which is supplemented by good illustrations, sets forth the possibilities of esophagoscopy and gastroscopy. Subjects related to medicine and of more than passing interest to the physician, such as evolution, medical ethics, climatology, are given considerable space. The biographical sketches are too brief and too dry to be any more inspiring than the bald statements to be found in any medical directory.

These volumes should be especially useful to men living far from medical libraries, for they are very complete in range of subjects and provide much information. It is to be regretted that in most of the contributions the references to original sources have either been entirely neglected or have suffered a very meager compilation.

*Clinical Hematology: An Introduction to the Clinical Study of the So-Called Blood Diseases and of Allied Disorders.* By GORDON R. WARD, M. D., Fellow of the Royal Society of Medicine, Medical Society of London, etc. Octavo of 394 pages, illustrated. Cloth, \$3.50, net. (Philadelphia and London: W. B. Saunders Company, 1914.)

This volume, according to the author, is primarily concerned with the clinical study of the so-called blood diseases, which has been overshadowed by exclusively pathological investigations; and secondly, it is concerned with a classification of the blood diseases necessary to an understanding of their nature. And yet the author has apparently overlooked the fact that the nature of the blood diseases cannot be clearly comprehended unless the fundamental pathological features are understood. The classification offered in the opening chapter is open to serious criticism, a fact which he recognizes but justifies on the basis that a bad one is better than none. In the first place, it is inaccurate and hence misleading. In the second place, it includes conditions which are not essentially blood diseases at all; and finally, well-known disorders, having a recognized pathological basis, are wrongly grouped. For example, hemochromatosis is considered



under the heading of a primary disorder, a red cell destruction, whereas the disease is regarded by most authorities as a primary disorder of metabolism in which, according to the work of Sprunt, there is no evidence of an abnormal breaking down of red cells. The newer work on Hodgkin's Disease, by Bunting, is not mentioned, the affection being classed as one primarily of the blood forming organs. Chlorosis and hemophilia are considered as primary diseases of the blood plasma, and pernicious anemia is said to be a disease characterized by increased red cell destruction and due "to a specific organism not yet isolated, its usual site of invasion being the alimentary tract." On the other hand, it would appear that the author does not consider pernicious anemia as a blood entity, for on page 360 he makes the statement that "the blood picture may be that of an Addisonian anemia or almost every variety of anemia that we can think of."

No parasitic diseases of the blood are considered. The section on the methods of blood examination is not complete, for the value of fresh blood studies is scarcely touched upon, nor can we agree with the statement that transitional cells are younger forms of neutrophilic leucocytes, or that any cell which is not a lymphocyte and has not a lobed nucleus is a large mononuclear.

Without wishing to be over-critical, it seems to the reviewer that the book abounds in misstatements which, though they may genuinely reflect the author's own views, are not in accord with those most generally accepted. The pictures, with the exception of two colored plates, are only fair, while those of the blood

cells on page 35 are very poor. Briefly, the author seems to be content with merely driving home clinical features without due regard for the pathological foundation of the diseases in question, from which alone we may ultimately hope for a satisfactory classification. It is to be hoped that a revision of the work will correct this evident lack of balance.

S. R. M.

*Military Hygiene and Sanitation.* By FRANK R. KEEFER, A. M., M. D. Cloth, \$1.50. (Philadelphia and London: W. B. Saunders Company, 1914.)

A text-book on military hygiene is peculiarly interesting at the present time, when the care of soldiers is occupying the attention of the civil and military authorities the world over, and this little publication from the pen of the Professor of Military Hygiene in the U. S. Military Academy at West Point, comes at an opportune moment. Its three hundred pages of fifteen chapters are devoted to the most important branches of this science, such as physical training, preventable diseases, clothing, water supply, etc. One chapter takes up especially the subject of venereal disease and another alcohol and other narcotics. The close association between drunkenness and venereal disease is well brought out and various remedies are suggested for the curtailment of the two evils. The book is systematically arranged, carefully written, and gives an excellent résumé of the important doctrines in military hygiene.

## BOOKS RECEIVED.

*The Clinics of John B. Murphy, M. D., at Mercy Hospital, Chicago.* Vol. III, No. 4. August, 1914. 8°. W. B. Saunders Company, Philadelphia and London.

*Manual of Obstetrics.* By Edward P. Davis, A. M., M. D. With 171 illustrations. 1914. 12°. 463 pages. W. B. Saunders Company, Philadelphia and London.

*Chemistry for Nurses.* By Reuben Ottenberg, A. M., M. D. 1914. 12°. 141 pages. Macmillan Company, New York.

*Practical Bandaging; Including Adhesive and Plaster-of-Paris Dressings.* By Eldridge L. Eliason, A. B., M. D. 155 original drawings and photographs. 1914. 8°. 124 pages. J. B. Lippincott Company, Philadelphia and London.

*Baltimore, Department of Health.* Department of Public Safety. Annual Report. Sub-Department of Health. To the Mayor and City Council of Baltimore for the Fiscal Year ended December 31, 1913. 1914. 8°. 782 pages. Baltimore.

*Infection and Resistance.* An Exposition of the Biological Phenomena Underlying the Occurrence of Infection and the Recovery of the Animal Body from Infectious Disease. By Hans Zinsser, M. D. With a chapter on Colloids and Colloidal Reactions by Professor Stewart W. Young. 1914. 8°. 546 pages. Macmillan Company, New York.

*The Pharmacy Handbook.* By F. W. Crossley-Holland, F. C. S. 1914. 12°. 224 pages. Henry Frowde and Hodder & Stoughton, London.

*Medical Jurisprudence.* A Statement of the Law of Forensic Medicine. By Elmer D. Brothers, B. S., LL. B. 1914. 8°. 301 pages. C. V. Mosby Company, St. Louis.

*Pathogenic Microorganisms.* By William Hallock Park, M. D., and Anna W. Williams, M. D. Fifth edition, enlarged and thoroughly revised. With 210 engravings and 9 full-page plates. 1914. 8°. 684 pages. Lea & Febiger, New York and Philadelphia.

*The Tonsils, Fauces, Lingual, and Pharyngeal.* With Some Account of the Posterior and Lateral Pharyngeal Nodules. By Harry A. Barnes, M. D. Illustrated. 1914. 8°. 168 pages. C. V. Mosby Company, St. Louis.

*Contributions to the Science of Medicine and Physiology.* By John C. Hemmeter, Phil. D., M. D., Sc. D., LL. D. Second series. Being a Collection of the Journal Publications of this Author from 1902 to 1914. Compiled by Thomas L. Patterson, M. A., and Charles C. Conser, M. D. 1914. 8°. Baltimore, Md.

*Food Products.* By Henry C. Sherman, Ph. D. 1914. 12°. 594 pages. Macmillan Company, New York.

*Quain's Elements of Anatomy.* Eleventh edition. Editors, Sir Edward Albert Schäfer, LL. D., Sc. D., M. D., F. R. S., Johnson Symington, M. D., F. R. S., and Thomas Hastie Bryce, M. A., M. D. In four volumes. Vol. II. Part II. *Splanchnology.* By J. Symington. With 349 illustrations. 1914. 8°. 392 pages. Longmans, Green & Co., London, New York, Bombay, Calcutta, and Madras.

*Local and Regional Anesthesia.* With chapters on Spinal, Epidural, Paravertebral, and Parasacral Analgesia, and on other Applications of Local and Regional Anesthesia to the Surgery of the Eye, Ear, Nose and Throat, and to Dental Practice. By Carroll W. Allen, M. D. With an Introduction by Rudolph Matas, M. D. Illustrated. 1914. 8°. 625 pages. W. B. Saunders Company, Philadelphia and London.

*Abdominal Operations.* By Sir Berkeley Moynihan, M. S. (London), F. R. C. S. In two volumes. Third edition, revised. Fully illustrated. 1914. 8°. Vol. I, 488 pages; Vol. II, 492 pages. W. B. Saunders Company, Philadelphia and London.

*The Clinics of John B. Murphy, M. D., at Mercy Hospital, Chicago.* Vol. III, No. 5. October, 1914. 8°. W. B. Saunders Company, Philadelphia and London.

*American Gynecological Society.* Transactions. Vol. XXXIX. For the year 1914. 1914. 8°. 520 pages. Philadelphia.



- A Manual of Bacteriology, Clinical and Applied.* By R. Tanner Hewlett, M. D., F. R. C. P., D. P. H. (Lond.). Fifth edition. 1914. 8°. 668 pages. C. V. Mosby Company, St. Louis.
- Operative Surgery of the Nose, Throat, and Ear.* By Hanau W. Loeb, A. M., M. D. In collaboration with Joseph C. Beck, M. D., R. Bishop Canfield, M. D., George W. Crile, M. D., Eugene A. Crockett, M. D., William H. Haskin, M. D., Robert Levy, M. D., Harris P. Mosher, M. D., George L. Richards, M. D., George E. Shambaugh, M. D., and George B. Wood, M. D. In two volumes. Vol. I. 409 illustrations. 1914. 8°. 390 pages. C. V. Mosby Company, St. Louis.
- Essentials of Physiology.* By F. A. Bainbridge, M. A., M. D. (Cantab.), D. Sc. (Lond.), F. R. C. P., and J. Acworth Menzies, M. D. (Edin.). With 134 illustrations. 1914. 8°. 434 pages. Longmans, Green & Co., London.
- The Cancer Problem.* By William Seaman Bainbridge, A. M., D. Sc., M. D. 1914. 8°. 534 pages. Macmillan Company, New York.
- Urgent Surgery.* By Félix Lejars. Translated from the seventh French edition by William S. Dickie, F. R. C. S. Third English impression. With 20 full-page plates and 1086 illustrations, of which 729 are drawn by Dr. E. Daleine and A. Leuba, and 198 are from original photographs. Vol. I: *Introductory, Head, Neck, Chest, Spine, Abdomen.* 1914. 8°. 614 pages. William Wood & Co., New York.
- University of Michigan, Contributions from the Pathological Laboratory.* Aldred Scott Warthin, Ph. D., M. D., Director. Reprints, Vol. VI, 1913-1914. 1914. 8°. Ann Arbor, Michigan.
- Carnegie Endowment for International Peace.* Founded December 14, 1910. Year Book for 1913-1914. 1914. 8°. 203 pages. Washington, D. C.
- The Brain in Health and Disease.* By Joseph Shaw Bolton, M. D., D. Sc. (Lond.), F. R. C. P. (Lond.). Longmans, Green & Co., New York; Edward Arnold, London.

- Bellevue and Allied Hospitals.* City of New York. Twelfth Annual Report. January 1, 1913, to December 31, 1913. 8°. 165 pages.
- The Pocket Formulary for the Treatment of Disease in Children.* By Ludwig Freyberger, J. P., M. D. (Vienna), M. R. C. P. (Lond.), M. R. C. S. (Eng.). Fourth revised and enlarged edition. Adapted to the British Pharmacopœia. With an appendix on Poisons, their Symptoms and Treatment. [1914.] 16°. 260 pages. Rebman Company, New York.
- The Salvarsan Treatment of Syphilis in Private Practice.* With Some Account of the Modern Methods of Diagnosis. By George Stopford-Taylor, M. D., M. R. C. S., and Robert William Mackenna, M. A., M. D., B. Ch. [1914.] 8°. 90 pages. Rebman Company, New York.
- The Backward Baby.* A Treatise on Idiocy and the Allied Mental Deficiencies in Infancy and Early Childhood. By Herman B. Sheffield, M. D. Awarded the Alvarenga Prize of the College of Physicians of Philadelphia, July 14, 1914. With 22 original illustrations in the text. [1915.] 8°. 184 pages. Rebman Company, New York.
- The Diagnostics and Treatment of Tropical Diseases.* By E. R. Stitt, A. B., Ph. G., M. D. With 86 illustrations. 1914. 12°. 421 pages. P. Blakiston's Son & Co., Philadelphia.
- Morris's Human Anatomy.* A Complete Systematic Treatise by English and American Authors. Edited by C. M. Jackson, M. S., M. D. 1182 illustrations, 358 printed in colors. Fifth edition, revised and largely rewritten. 1914. 4°. 1539 pages. P. Blakiston's Son & Co., Philadelphia.
- Progressive Medicine.* A Quarterly Digest of Advances, Discoveries and Improvements in the Medical and Surgical Sciences. Edited by Hobart Amory Hare, M. D., assisted by Leighton F. Appleman, M. D. Vol. IV. December, 1914. 8°. 413 pages. Lea & Febiger, Philadelphia and New York.
- American Proctologic Society.* Transactions of the Sixteenth Annual Meeting. Held at Hotel Chalfonte, Atlantic City, N. J., June 22 and 23, 1914. 8°. 157 pages. St. Louis, Mo.

## NEW PUBLICATIONS.

The following six monographs:

- Free Thrombi and Ball-Thrombi in the Heart. By J. H. HEWITT, M. D. 82 pages. Price, \$1.00.
- Benzol as a Leucotoxin. By LAURENCE SELLING, M. D. 60 pages. Price, \$1.00.
- Primary Carcinoma of the Liver. By M. C. WINTERITZ, M. D. 42 pages. Price, 75 cents.

- The Statistical Experience Data of the Johns Hopkins Hospital, Baltimore, Md., 1892-1911. By FREDERICK L. HOFFMAN, LL.D., F.S.S. 161 pages. Price, \$2.00.
- The Origin and Development of the Lymphatic System. By FLORENCE R. SABIN. 94 pages. Price, \$2.00.
- The Nuclei Tubæris Laterales and the So-called Ganglion Opticum Basale. By EDWARD F. MALONE, M. D. Price, \$1.50.

are now on sale by THE JOHNS HOPKINS PRESS, Baltimore. Other monographs will appear from time to time.

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# BULLETIN

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## RENAL CANCER ASSOCIATED WITH RENAL STONE.\*

By JOHN R. CORYELL, M. D.,  
*Mayo Clinic, Rochester, Minn.*

The object of this paper is not to advance a new theory nor to discredit an old one, but to record the macroscopic and microscopic findings in kidneys, the seat of both stone and cancer.

The method of procedure has been as follows:

1. Review of the primary pathologic diagnosis which was made on frozen sections stained with Unna's polychrome methylen blue in the diagnostic laboratory immediately after removal of the organ.

2. Study of the gross specimen.

3. Microscopic examination of sections from cortex, medulla and pelvis of specimens kept in 10 per cent formalin, frozen and stained with hematoxylin and eosin; also of serial paraffin sections of many specimens stained with Sudan III and Scharlach, and with Weigert and Van Gieson.

The study covers all cases of renal cancer and renal stone from which tissue was removed in the Mayo Clinic from January 1, 1905, to July 1, 1914, a total of 145 cases, of which 131 were of stone only, 5 of cancer only, and 9 of cancer associated with stone.

\* Submitted for publication, November 6, 1914.

### CHRONIC IRRITATION FROM RENAL STONE.

A great deal has been written on the relation between chronic irritation and the formation of cancer. That the two processes are frequently associated cannot be questioned. Whether cancer is the direct result of chronic irritation, or whether the latter plays the part of an extraneous exciting agent and determines the localization of the former in an organism which contains some sort of a chemical sensitizing substance (Loeb), or is influenced by some hereditary factor (Slye), is still an open question.

The expression, chronic irritation, is very broad in its scope and includes, under a single term, conditions induced by mechanical agents, as trauma, pressure (continuous or intermittent), friction, shock, dust, smoke, and foreign bodies of every kind as well as organisms living or dead; chemical agents, notably those concerned in the so-called occupational cancers of dye- and paraffin-workers and of chimney-sweeps; and physical agents, as heat, X-rays, light, electricity.

In 1823, Breschet and Ferrus stated their opinion that cancer invariably succeeded irritation or inflammation, and was



incapable of being developed except in places where one or other of those states had pre-existed (Walshe).

Virchow, in the early sixties of the last century, sought to explain the inception and development of cancer by irritation starting the cells upon a career of lawless growth. To-day Virchow's theory is accepted by many investigators as an explanation—to a certain degree—of the etiology of malignant proliferation.

Trauma, as a form of irritation, has been observed by Coley, who in 1911 reported personal observations on 250 cases of carcinoma, in which there was a history of trauma in 32.8 per cent. He refers to the work of Röpke who, in 1905, in a study of the material at the Surgical Clinic of Jena, collected statistics of 800 carcinomas "plus a larger number of cancers associated with chronic irritation," showing that in carcinoma chronic irritation seems to play the more important rôle. Ziegler states that of 170 cases of carcinoma, 37 of the patients, or 22 per cent, gave a history of a single antecedent trauma; Estlander gives 59 cases with 15 antecedent traumas (25.4 per cent); Snow 22 per cent in 143 cases; Henry 16.8 per cent in 196 cases—all preceded by a single trauma.

Levin, in 1910, published a table of 2882 cases of cancer involving different parts of the body. In 545, or 19.2 per cent, there was a definite history of previous local reaction.

The following are the principal reported examples of cancer developing at the site of irritation of varying duration and intensity:

Cancer of the uterus in women who have borne children, more common than in virgins.

Cancer of the cheek associated with the eating of very hot rice in certain provinces of China.

Cancer of the abdomen subsequent to burns from the Kangri or charcoal stove worn by the people of Kashmir.

Epithelioma of the mucous membrane of the mouth associated with chewing betel-nut mixed with lime—which is very irritating—by Hindoos.

Cancer of the penis developing on a chronic balanitis or unrelieved phimosis.

Gastric cancer developing on gastric ulcer (Wilson and MacCarty). "Hauser was the first to show that in gastric ulcer new tubular glands are formed, which are lined by cylindrical cells and may undergo cystic dilatation; and to call attention to the development of gastric cancer on a gastric ulcer" (Wilson). The most recent compilation of statistics from operative material shows that approximately 57.4 per cent of the gastric carcinomas develop on a gastric ulcer (Wilson and McDowell). Moynihan gives 60 per cent; Mayo Robson 59 per cent.

In an examination of 5000 appendices in the Mayo Clinic, 22 were found to have developed cancer. "Obliteration of lumen occurred in 22.8 per cent, and 90 per cent of the carcinomas occurred in partially or completely obliterated appendices. All were associated with chronic inflammation" (MacCarty and McGrath).

Of 27 colons with diverticulitis, 11 had cancer engrafted on them (Telling, quoted by Giffin and Wilson).

Cancer of gall-bladders previously affected with gall-stones.

"In nearly all of the cases of our own series, gall-stones were present" (Mayo).

Cancer of the lip in smokers.

Tumors of the bladder, benign and malignant, in aniline dye-workers.

Cancer among X-ray workers.

Cancer of the breast after chronic mastitis.

Epithelioma after lupus or tuberculosis of the skin (L. Savatard).

Sarcomatoid hyperplasia of lymph nodes in tuberculosis.

Hypernephromas preceded by renal calculi (Ewing).

Cancer of the scrotum in chimney-sweeps and in paraffin workers.

Epitheliomas of the eye-lids. Fisher reports that of 88 cases, 46 per cent were in the lower lid and 36 per cent at the inner canthus. "These parts are usually hyperemic when the upper lid and outer canthus show comparatively little evidence of irritation. They are more frequently irritated by tears and foreign matter."

Rodent ulcer succeeding a hard pimple near the angle of the eye (Hutchinson).

Cancer on the margin of the lower lip, developing from a "crust."

Cancer from warts, cutaneous horns, sebaceous cysts, papillomas and ulcers (simple or specific) of the skin.

Cancer of the skin developing in tar, carbon and asphalt workers.

Prostatic cancer beginning where a chronic prostatitis is present (Young).

Local trauma of any kind (Coley).

Epitheliomas developing at the base of the right horn of cattle used to haul carts by a rope fastened to the right horn.

Cancer in horses where the bit irritates the corners of the mouth (Plicque).

Subcutaneous fibromas under the collar and girth of horses (Plicque).

Carcinoma of the posterior mammae of dogs, the ones most frequently congested (Plicque).

Cancer of the upper lip of cats, the one more likely to be wounded.

Papillary epitheliomas on the tongues of rats fed for a long time on oats (Stahr).

Ribbert obtained small but typical papillary growths on the inner surface of the rabbit's lip by repeatedly scraping certain parts, again denuding them as soon as the epithelium was regenerated and finally allowing them to heal.

Clunet produced sarcoma in the rat by repeatedly exposing it to X-rays.

Rous has shown that more rapidly growing tumors developed at the site of a trauma than elsewhere in the body.

Kelley refers to papillomas developing on sheep's noses from grazing upon short stubble.

Perhaps the first to call attention to the pre-cancerous condition of the cell was Hutchinson, who spoke of it 50 years ago (Wood). Ribbert, in 1901, emphasized the importance of this stage of the cell.



Levin succeeded in increasing the susceptibility of rats to sarcoma by previous local irritation from injections of scarlet red and ether and established "the first experimental proof of the existence of a local 'pre-cancerous stage.'"

In kidneys, which are the seat of stones, one of the earliest changes is a proliferation of fibroblasts beneath the tubular epithelium. The new tissue thus produced apparently causes an upset of the balance between the epithelium and the connective tissue, which is followed by a proliferation of the epithelium. Here, at least, the epithelial multiplication seems to be due to a chronic irritation, set up by the stone. Thiersch accepts the pathologic condition in the connective tissue as causing it to become less resistant against the epithelial cells. "The epithelial growth follows the analogy of normal gland formation; while, owing to a process of adaptation to the abnormal environment and loss of function, the atypical structure of cancer results" (Ewing). Ewing refers to Hansemann, who uses the term "anaplasia" in conditions of tumor-cell changes which show unequal, asymmetrical and multipolar mitoses and destruction of chromosomes of frequent occurrence, particularly in the more malignant tumors. More or less anaplastic cells occur in inflammatory processes—cells with irregular mitoses. This strengthens the theory of the relationship between chronic irritation and tumor formation. Further, gametoid mitosis has been brought about in plants by means of chemical irritants, which would seem to add even more evidence to this theory.

In some of the sections of kidneys from cases of renal stone associated with renal cancer, there seems to be a tendency on the part of the cancer cells to mimic the renal tubules. In places, the epithelial cells supported by a delicate framework of connective tissue are arranged in columns, the central cells of which have apparently undergone degeneration and absorption, thus giving an appearance somewhat similar to that of renal tubules. The tubules are obviously of neoplastic origin; the component cells are distinctly cancerous and the general and minute appearance is different from that of regenerating tubules (Fig. 1). In this case the cancer was limited to and derived from the renal pelvis.

In several sections of kidneys containing stones are seen regenerating tubules. Their appearance, with both the low and high power, is embryonic. The newly formed or regenerating tubules are often surrounded by a small amount of delicate strands of connective tissue, supporting capillaries and at times slightly infiltrated with lymphoid cells. These tubules are somewhat narrower than the mature ones. The lining cells are proportionately larger than those of the epithelial lining of fully developed tubules. The nucleus is large and stains readily with hematoxylin; and at times nucleoli may be seen. The nuclear and cell membranes are distinct. Some cells contain two nuclei, but no chromosomes or early mitotic figures are seen (Fig. 2).

In kidneys, the seat of stone and cancer, where the cancer is not actually invading the substance of the gland, but where it is separated more or less completely by bands of connective tissue or by blood-vessels (Figs. 3 and 4), the preparatory

inflammatory changes, *i. e.*, the formation of fibroblasts, new capillaries and lymphoid infiltration—which is often marked—seem to be entirely apart from the neoplasm. In other areas, where the inflammatory changes seem to be absent, or of a lesser degree, cells which are with great difficulty distinguished from neoplastic cells are present in varying numbers, interspersed among the connective-tissue cells. Whether these are embryonic connective-tissue cells or precursors of cancer cells it is almost, if not quite, impossible to decide. "Inflammatory hyperplasia passes by insensible gradations into a neoplastic growth" (Ewing). In places, at the periphery of the cancer, there is a network of fine connective tissue and in some places engorged capillaries. In the meshwork of connective tissue, as a rule, lymphoid cells predominate, but in many places there are cells which, although probably inflammatory in character, are with difficulty assigned to the group of neoplastic cells or to that of inflammatory ones. Their protoplasm stains with varying degrees of intensity with eosin; at times it is finely granular, at others it is clear and sometimes vacuolated. The nucleus usually stains deeply with hematoxylin, showing a well-defined border and a nucleolus. The cell outline is usually distinct. The shape of the cell is frequently modified by pressure—one often sees round, polygonal, fusiform and even flattened cells. When pressure is absent, the cell is usually round. In size, the cells vary somewhat, but are usually about 15 microns in diameter. In other words, in the same section one may see cells which are normal, others which are inflammatory, and still others which, apparently as a result of prolonged irritation, are distinctly neoplastic in character. If there is a line of demarcation between certain stages, or phases, of a chronic inflammatory process and neoplastic formation, it is, at times, very indistinct and it is difficult, if not impossible, to say where normal evolution stops and neoplasm begins (Fig. 5). Or, in other words, the stages of development of a cell under the influence of, or as a result of, an irritation, which is constant and prolonged, seem to be (1) normal, (2) inflammatory, (3) hyperplastic, or (4) neoplastic (either benign or malignant).

In all of the cases studied one may see destruction of the kidney, varying in degree from an involvement of a small portion in some to that of the entire organ in others. In those in which some of the parenchyma is left, there may be seen an interstitial and a parenchymatous nephritis; and in some of the specimens are seen areas of lymphoid infiltration, the central parts of which have undergone necrosis. In other areas are polymorphonuclear leucocytes, denoting abscess formation. Interstitial changes vary from 1 to 4 on a scale of 4, parenchymatous from 1 to 3 on a scale of 4 (Fig. 6). In kidneys, the seat of stones, in many places the epithelial cells lining the tubules show different stages of degeneration, having lost their vigor. There is frequently seen hyperplasia of the connective tissue, and the epithelium may have undergone (1) necrosis, (2) cyst formation and, in some specimens, (3) malignant metamorphosis. Notwithstanding the work of Kleinschmidt, who says, "Inflammatory changes of the kidney or pelvis of the kidney are not found in my cases," in



every case examined, 140 in all, not only in cases of renal stone associated with cancer, but also in kidneys containing only stones, inflammatory changes are seen. They were found in the parenchyma in some cases, in others the process was limited to the pelvis, and in still others both were involved. The type of inflammatory reaction varied from that of an acute process in some to a well-marked chronic type in others (Fig. 7).

In several specimens the tubules are dilated in varying degrees, some being 4 or 5 times their normal size, and cysts are seen, but not frequently.

Stone-pockets are very commonly observed. Some are microscopic in size. Other kidneys consist entirely of connective-tissue stone-pockets (Fig. 8). The walls of the stone-pockets are made up of connective-tissue stroma with lymphoid infiltration lined with 2 or 3 layers of cuboidal, or, in some places, flat cells.

Varying amounts of fat are not infrequently found in the pelvis of kidneys containing stones. Braasch has called attention to this fact. Smooth muscle fibers are not infrequently seen in the parenchyma of kidneys containing stones. In several specimens of this series may be seen spindle cells with long nuclei, the protoplasm of which is usually granular and stains readily with eosin. Some of the nuclei are oval, others are very long and rod-shaped. These obviously belong to smooth muscle fiber. An explanation of the occurrence of the smooth muscle fibers is found in the fact that in foetal life the kidney is very rich in smooth muscle, whereas in adult life it is found only in the capsule and wall of the pelvis. The collecting tubules, derived from the Wolffian duct, are surrounded by smooth muscle fibers in early foetal life. These fibers disappear as development advances. At times, this disappearance may be incomplete and small rudiments of smooth muscle fiber may occasionally remain in the pyramids (Nicholson). In some of the sections studied, these fibers are also seen in the medulla and cortex. Nicholson says that the muscle comes from the layer of cells which also forms the renal epithelium. This, as shown by Huber, is the mesoblast. Areas in which development has been arrested at an early period may contain the mother-cell of the epithelium and of the plain muscle.

In squamous epitheliomas arising from the pelvis, of which there are five definite cases in this series, the origin of the neoplasm is probably from the epithelium of the renal pelvis (Figs. 9 and 10). The renal pelvis is derived embryologically from the Wolffian duct, which is derived, in part at least, from the epiblast. Epiblast almost always gives rise to squamous epithelium; therefore, it is at least possible that squamous epitheliomas are developed from the epithelium of the renal pelvis. Stoerck says that tumors starting in the renal pelvis are usually associated with conditions of chronic irritation, as, for example, from stones.

In one case of cancer associated with stones the neoplasm started in the epithelium lining the tubules. In this particular case it was not ascertained at which part of the tubule the cancer took its origin, but from the glomeruli to the end

of the collecting tubules the lining epithelium had undergone various degrees of degeneration and in different places along the tubule hyperplasia of the epithelium was seen. In one case (Fig. 11) the tubular "offshoot" was malignant. Thus we see that cancer of the kidney which contains stone may arise from the tubules. In some of these cases, colloid degeneration is seen (Fig. 12). At times the stones are limited to the parenchyma (Fig. 13). Here the stones are shown in the tubules. There were none in the renal pelvis in this case.

The origin and character of a cell, not infrequently found in kidneys affected with stones, and which occurred in 28 cases in a series of 140, has been somewhat difficult to determine. In some specimens it was not commonly seen; in others it was of very frequent occurrence and was even found in groups in several specimens. It was a large refractile cell, about 20 to 30 microns in diameter. The cell membrane was usually distinct, but at times invisible. With the hematoxylin and eosin stain, the protoplasm was very pale, practically white or at most a pale pink, occasionally clear but usually granular, and some of the cells contained vacuoles. The nucleus, not always present and at times fragmented, was usually about 3 to 4 microns in diameter. It stained with a varying degree of intensity, at times quite deeply. Its border was usually well defined. No mitoses were seen in these cells. In general arrangement, these cells frequently gave an appearance somewhat resembling that of a mesothelioma (so-called hypernephroma). They were often arranged in columns along fine strands of connective tissue, which, at times, supported engorged capillaries (Fig. 14). The engorged capillaries, however, were of infrequent occurrence. In many specimens lymphoid cells were seen, varying in number from a few cells to a marked infiltration, among the clear cells. Fibroblasts were also seen scattered among the delicate strands of connective tissue. In some of the sections were red blood cells interspersed among the clear cells. In some places these groups of cells were surrounded by well-defined bands of connective tissue; in others, a few of the clear cells were found scattered between the renal tubules. Several sections showed cells somewhat similar to these, but they were found in infarcts; were apparently derived from connective-tissue cells and were probably largely hydropic in character, since they contained very little fat. From the large, deeply-staining nucleus, distinct nuclear and cell membranes, and the fact that the protoplasm was light in many cells, it was presumed that the cells just described were embryonic in character.

Zebbe describes similar cells and says they may arise from connective tissue, endothelium or from phagocytes; that they are found in large white and contracted kidneys, but not in acute nephritis nor in diabetics; that they are similar to cells found in the lung and thyroid and Grawitzian tumors (mesotheliomas); and that they are peculiar to the kidney under certain conditions.

Fig. 15 shows this cell in an early stage of development. Here it seems to be in a renal tubule, in which all of the cells are of the same type. They contain granules which stain with fat stains, as do the cells from other cases which are more



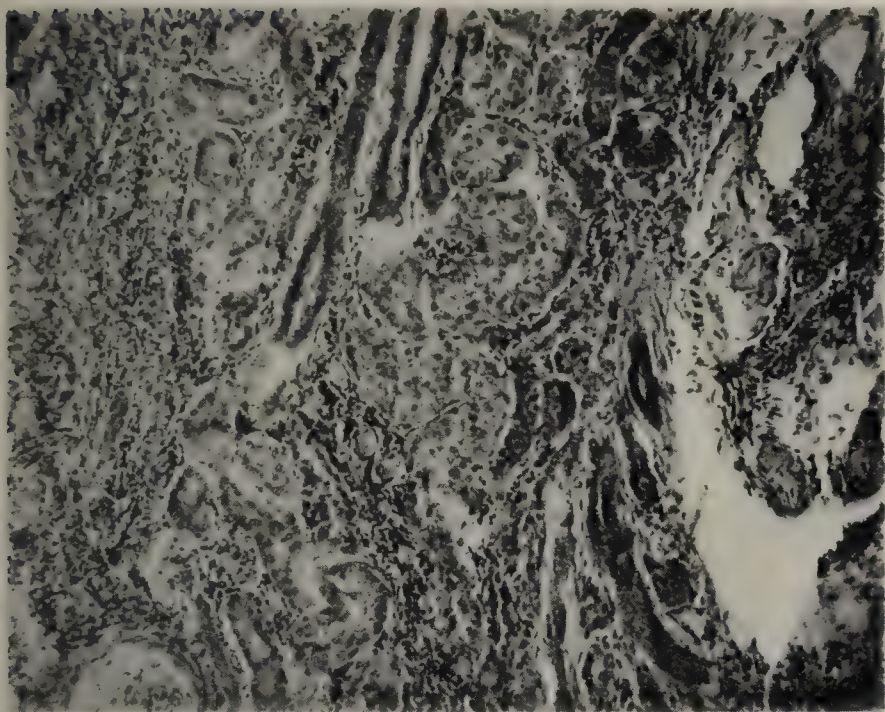


FIG. 1 (A2662).  $\times 120$ . Attempt of cancer cells to mimic renal tubules in their arrangement.

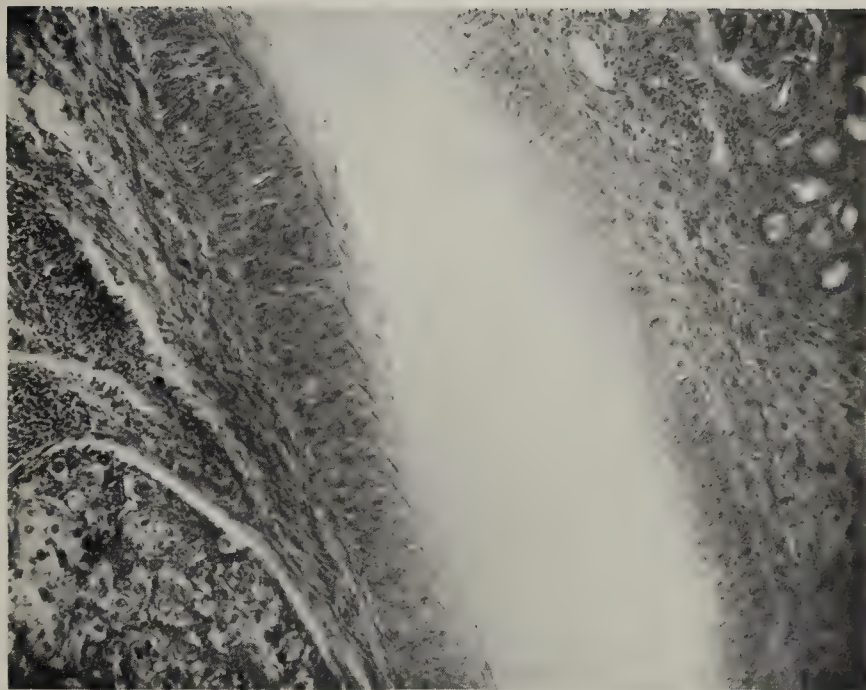


FIG. 3 (A49100).  $\times 50$ . Renal substance (glomeruli and tubules) with a large artery separating it from a cancerous area.

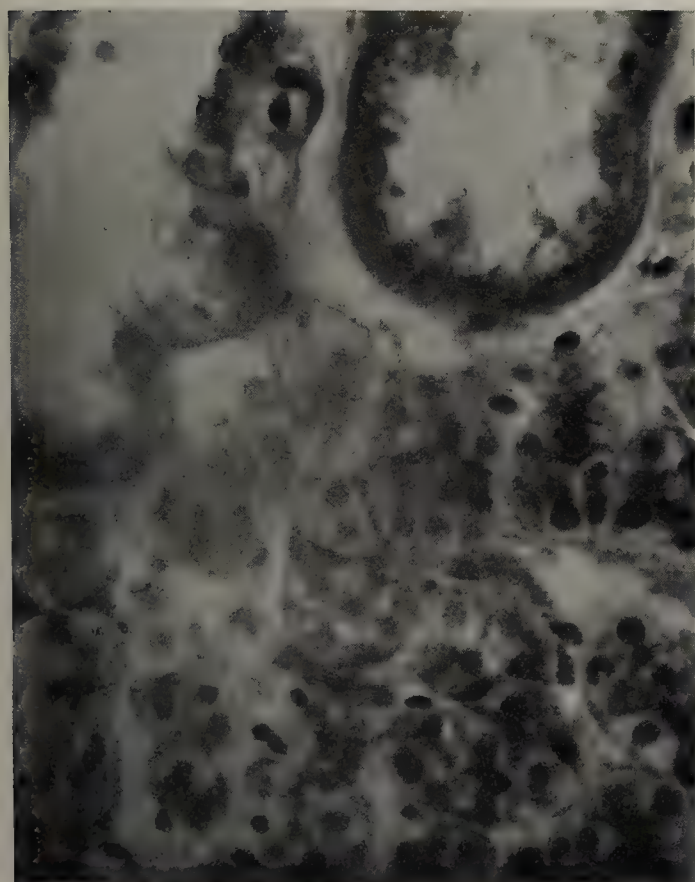


FIG. 2 (A91687).  $\times 250$ . Regenerating renal tubules, showing embryonic character of the cells. Large, deeply-stained nuclei in lower right corner. Above are old tubules, cut longitudinally, showing disintegrating cells.

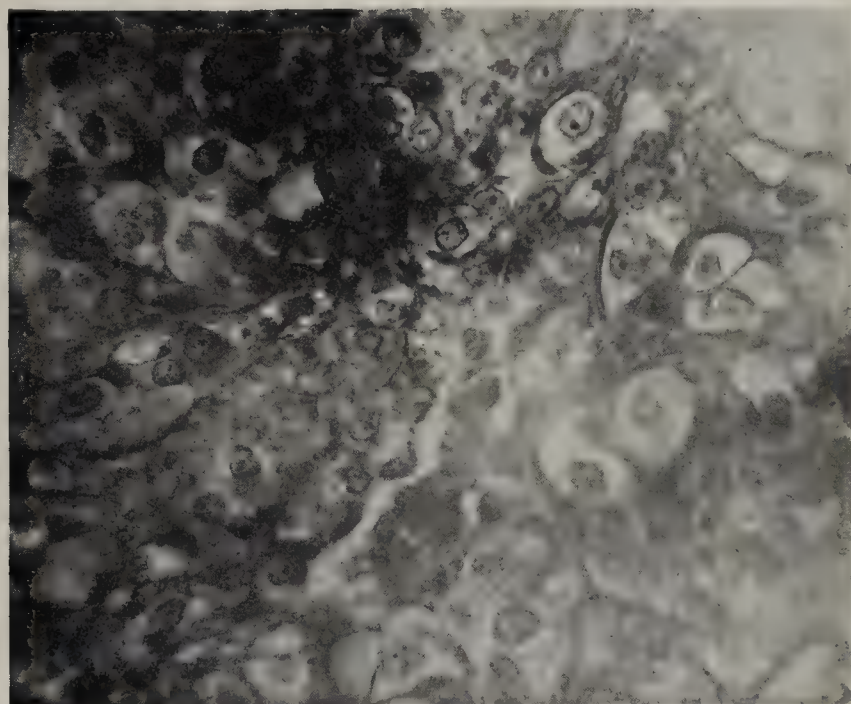


FIG. 4 (A49100).  $\times 250$ . Cancerous area shown in Fig. 3. Large polyhedral cells, 20 microns in diameter; pale-staining, slightly eccentric nuclei; very little intercellular substance.







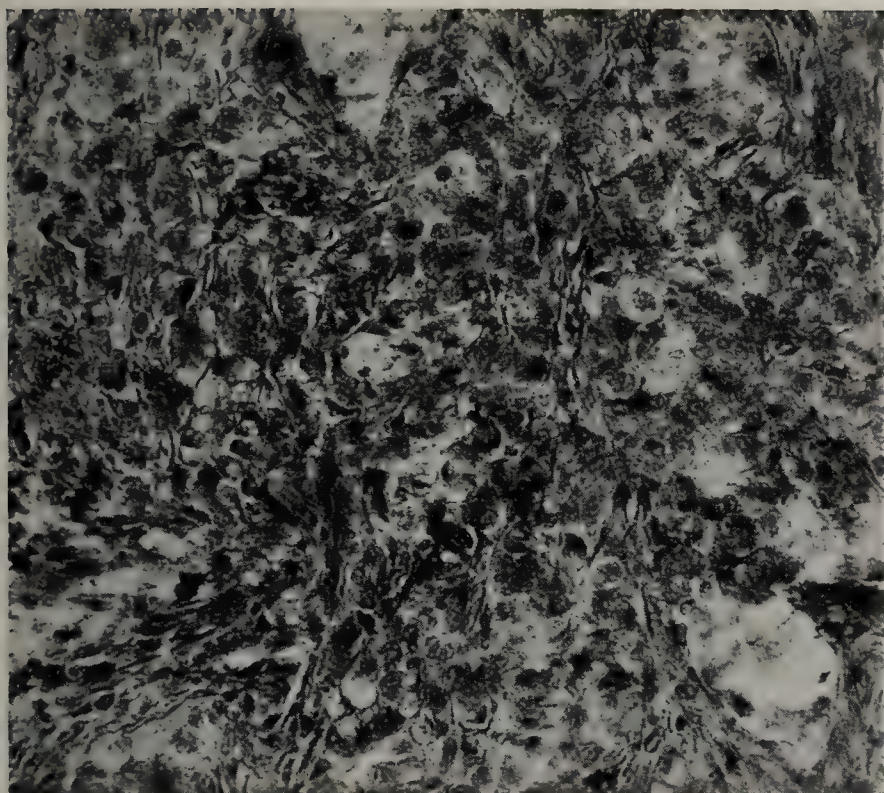


FIG. 5 (A7569).  $\times 250$ . Section through area of inflammatory and neoplastic cells. Tubules very small and greatly diminished in number. The lining cells spherical, with large deeply-stained nuclei; scanty protoplasm, surrounded by well-defined strands of connective tissue with oval nuclei. At other times, they are disposed irregularly. Cancer cells at times mimic the renal tubules in their arrangement of cells supported by delicate threads of connective tissue. The cells are polygonal; protoplasm very finely granular; limiting membrane distinct.

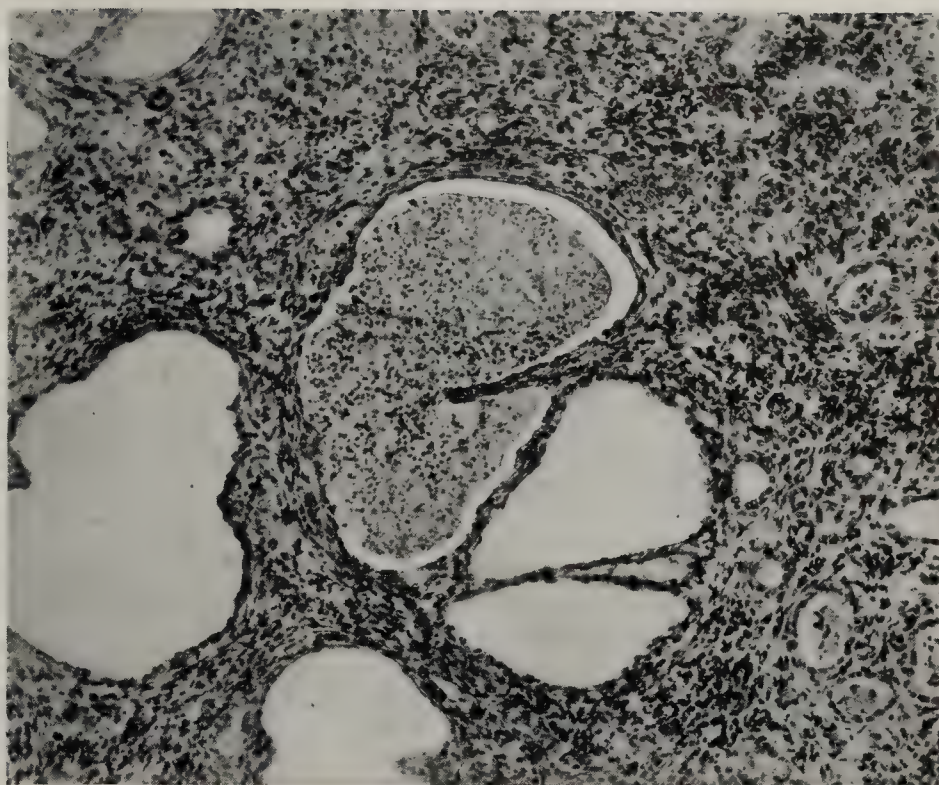


FIG. 7 (A73915).  $\times 120$ . Section of kidney. Dilated tubules contain pus, polymorphonuclears and debris. Walls of connective tissue with 1 to 3 layers of cuboidal cells whose nuclei are deeply stained; very little protoplasm.

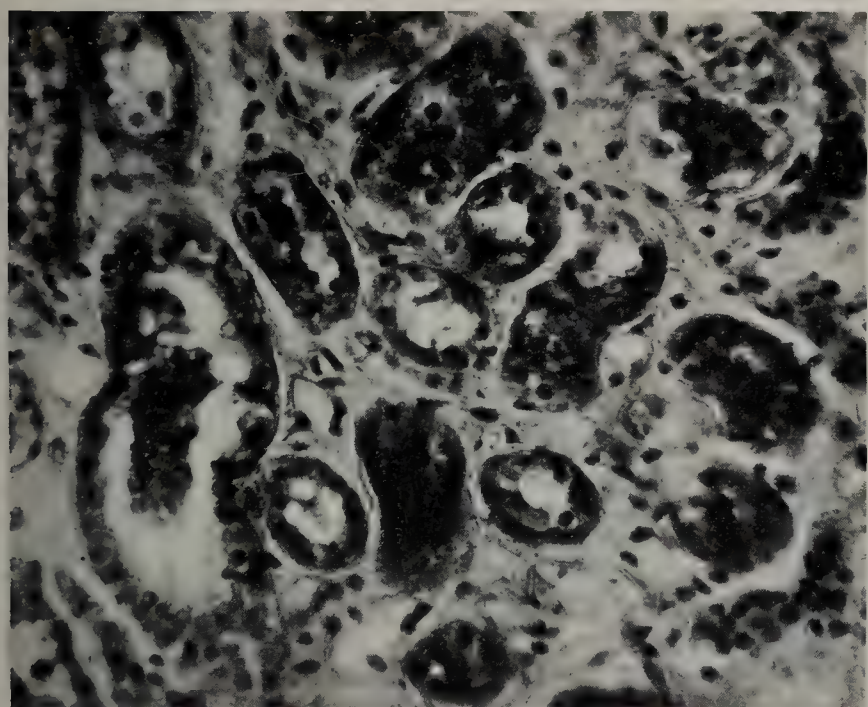


FIG. 6 (A75806).  $\times 50$ . Through an area of cut-off degenerating renal tubules. Shows disintegrating cells lining the tubules; nuclei indistinct. Protoplasm granular; marked increase in connective tissue.

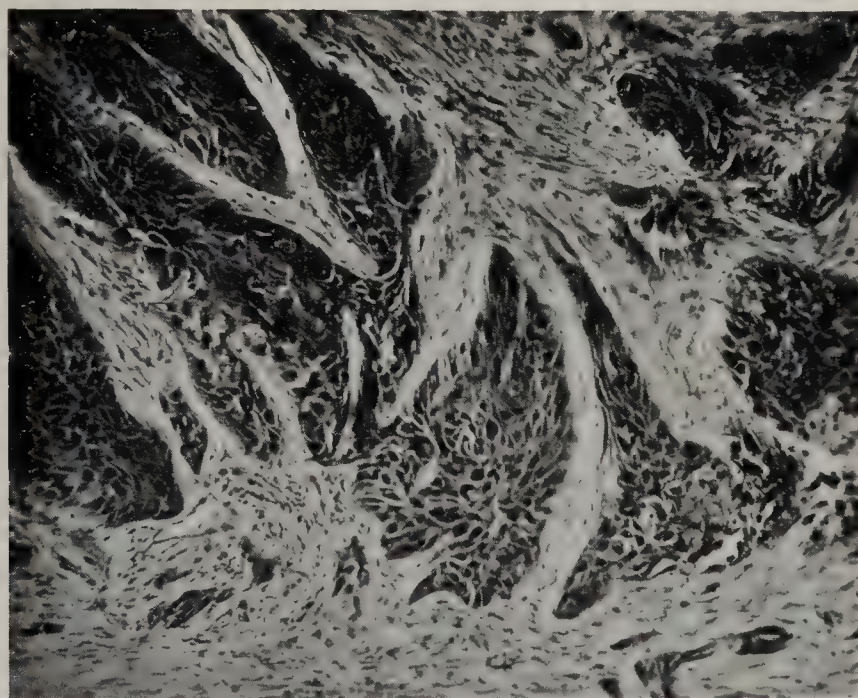


FIG. 9 (A3809G).  $\times 100$ . Section through squamous-celled carcinoma of renal pelvis. Shows arrangement of cancer cells and connective tissue.









FIG. 8 (S2907). Left kidney one-third normal size. Fat and fibrous tissue throughout. Stones and stone-pockets throughout.

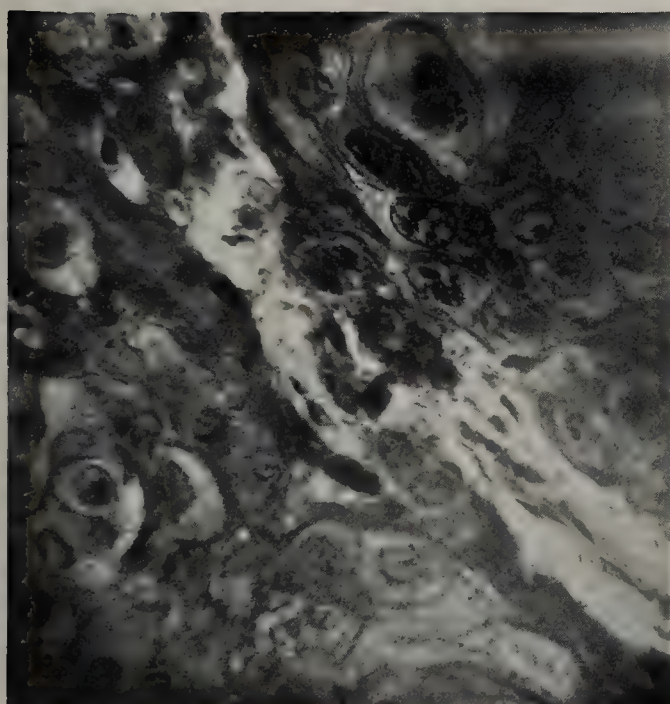


FIG. 10 (A23253).  $\times 250$ . Squamous-celled cancer with hyaline degeneration.

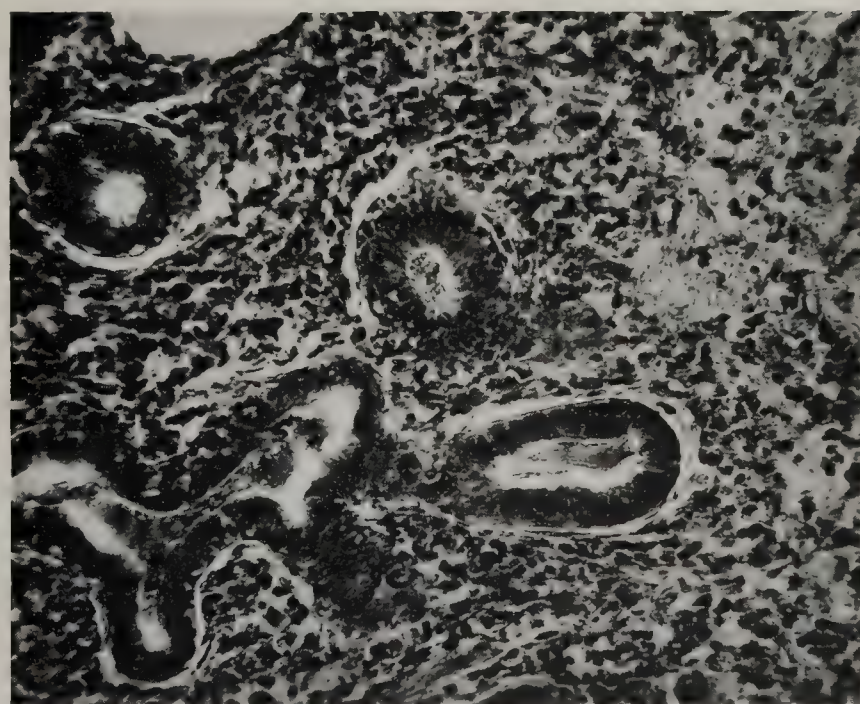


FIG. 11 (A74679). Cancer originating in the tubules; chronic parenchymatous nephritis (2); chronic interstitial nephritis (2); suppurative nephritis 1. 150 D. mag. of area showing branching cancer tubules, the lining cells of which appear to be invading the stroma. It also shows lymphoid infiltration.







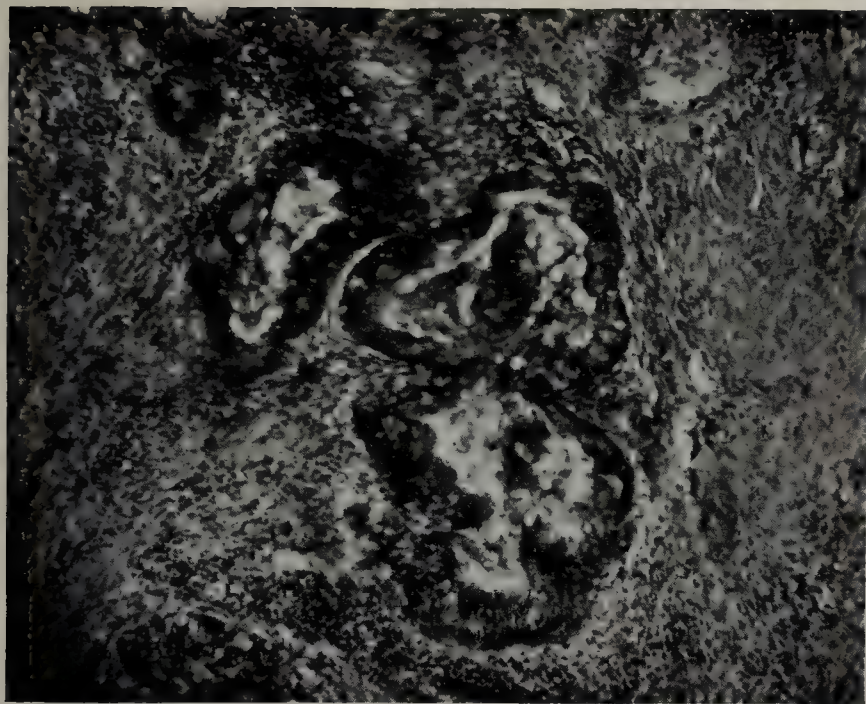


FIG. 12 (A91370).  $\times 150$ . Section of papillary adenomatous type of cancer with cells forming acini filled with colloid substance. The cells are supported by delicate strands of connective tissue; the latter sends in strands which, covered with cells, give a papillary appearance. Lymphoid cells are scattered between the acini.

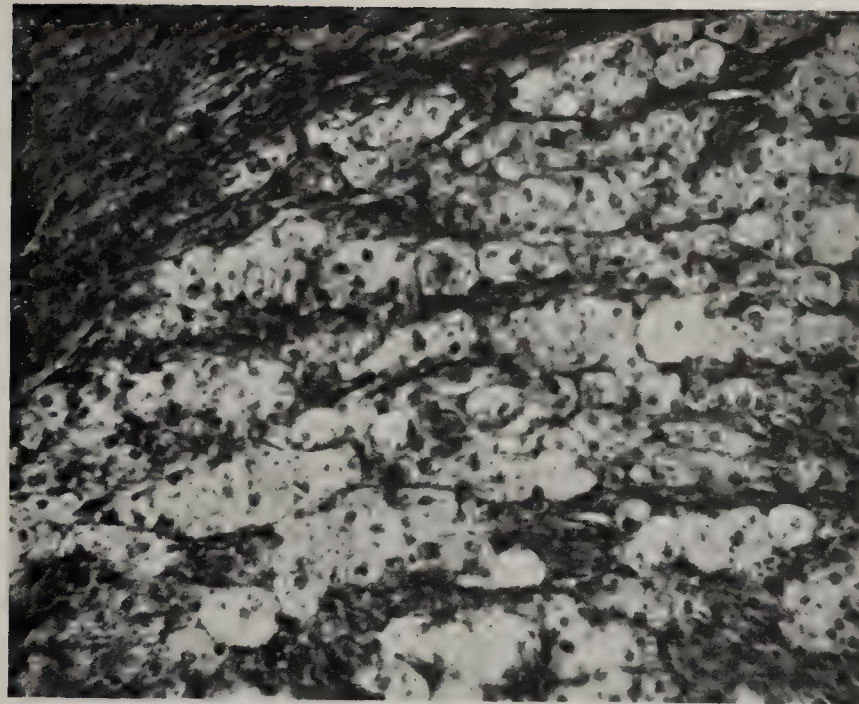


FIG. 14 (A69689).  $\times 250$ . Section through area of "fat-hydronic" cells arranged in columns, suggesting a mesothelioma. Cells supported by strands of connective tissue, in which are seen lymphoid cells.

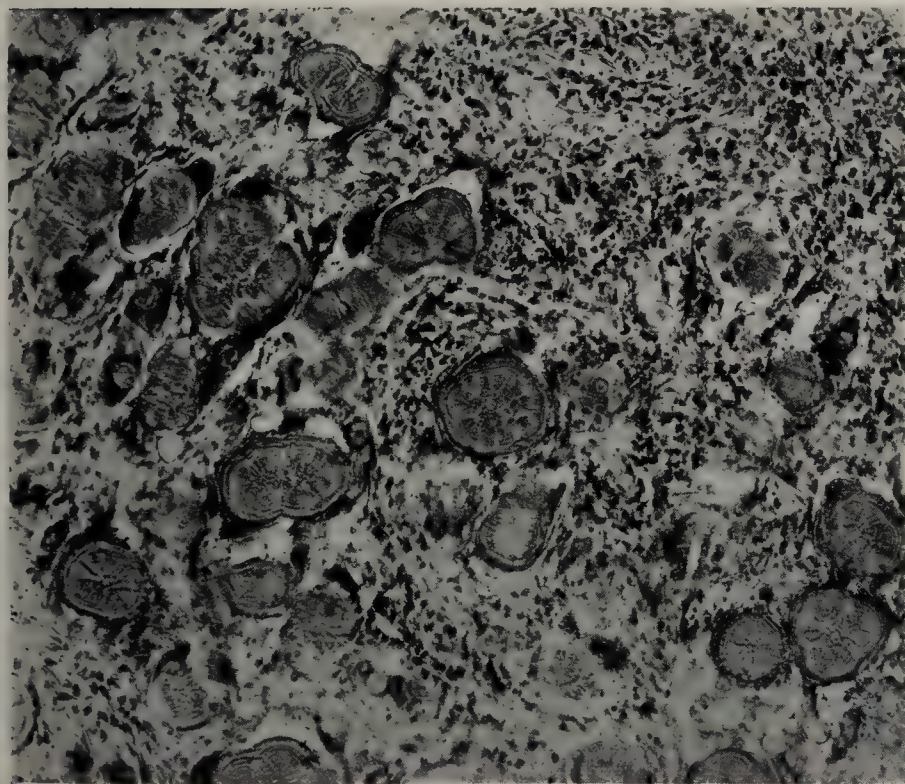


FIG. 13 (A86712).  $\times 120$ . Section through tubules containing stones. Tubules lined with flattened cells, 1 to 2 layers. Stroma increased; lymphoid infiltration. Stones dark brown in color; concentric lamellæ; radial striations.

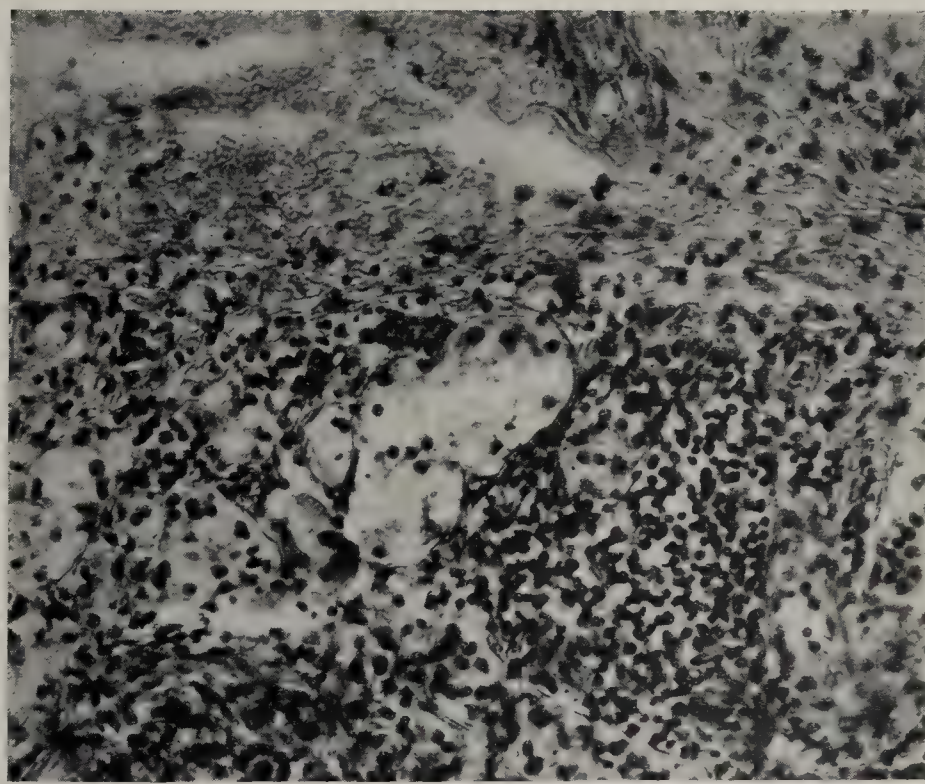


FIG. 15 (75542).  $\times 250$ . Early stage of "fat-hydronic" cells seen in the renal tubules (fat stain).







advanced (Fig. 14), and are arranged in masses or columns. They are not found in normal adrenals, but are similar to cells found in mesotheliomas. They are found in the kidney, are of renal origin and appear to come from the renal tubules. They are found in kidneys containing stones and also in kidneys containing stones and cancer.

TABULATED SUMMARY OF CASES OF RENAL CANCER ASSOCIATED WITH RENAL STONE REPORTED IN THE LITERATURE.

Author.	Number of Cases.	Cancer.	Stone.
Ransohoff.	1	Duration 12 mos.	Duration much longer.
Noble and Babcock.	1?	Papillary, in pelvis.	
Albarran and Imbert.	Collected 23, 3 personal.	All in adults.	
Nicholich.	1	Papillary, in pelvis.	Several.
Minet.	3	Papillary, in pelvis.	Multiple.
Oraison and Nodal.	2		
Porter.	1		53 yrs. history. Wt. 1920 gr's Ureter.
Deaver.	1	Ureter.	
Rafin.	3	1. Epithelioma. 2. Mesothelioma. 3. ?	
Lacassagne.	1	Pelvis.	

In reporting the foregoing cases, the authors dwelt largely on the clinical problems and very little on the pathologic aspects. It is at once seen that cancer associated with stone in the kidney is not of common occurrence, 3 being the largest number of cases hitherto reported by any one author. Albarran and Imbert collected and reported 26 in two or three hundred cases of renal tumors.

In the Mayo Clinic, since April 5, 1905, that is, in 9 years and 6 months, there have been removed 140 kidneys containing stones, and of these, 9 also contained cancer, or about 6.5 per cent. During the same period, 6 nephrectomies were done for cancer of the kidney, one of which was metastatic. The proportion, therefore, is 9 cancers of the kidney associated with stones to 5 cancers without stones, or 64+ per cent for the former and 35+ per cent for the latter. This is about the same as in gastric cancer developing on a gastric ulcer and of other cancers developing at the site of chronic irritation.

Tuberculosis was found in only one of the 140 kidneys containing stones.

Amyloid degeneration was found in four cases.  
Polycystic kidney was found in one case.

The equilibrium or mutual counteraction between remission of cell multiplication and indefinite reproduction is very sensitive; and until this is better understood, the nature, development and treatment of cancer will remain an enigma. Until the origin and development of cancer has been assigned to some definite cause, individuals will continue to accept or to reject theories according to their own ideas. Certainly some are improbable, while, on the other hand, some have all the appearance of probability and seem almost certainly true. From the above study, therefore, it has seemed useless even to attempt a consideration of the relative merits of the different

hypotheses. However, from a clinical and more particularly from a pathologic study, one must admit that irritation is a strong etiologic factor in the development of renal cancer.

SUMMARY.

1. Renal epithelium (tubular and pelvic) not infrequently regenerates.
2. Renal tubules regenerate not infrequently as a whole.
3. The stages of development of renal epithelium under the influence of or as a result of irritation which is constant and prolonged are (1) normal, (2) inflammatory, (3) hyperplastic, (4) neoplastic (which may be either benign or malignant). In the kidney there seems to be no distinct line of demarcation between certain stages or phases of a chronic-inflammatory process and neoplastic formation, and it is impossible to say where normal processes cease and neoplastic processes begin.
4. The preparatory phenomena of renal new-growth seem to take place not in the area actually irritated, *i. e.*, not in the area which shows actual inflammatory reaction, but just beyond the same.
5. Even if heredity plays the same rôle in human cancer as it seems to play in mouse cancer, chronic irritation in the kidney is still of very great importance, in that it determines the location of the neoplasm.
6. There is, at times, an attempt on the part of the neoplasm to mimic the structure of the kidney by a columnar arrangement of cells and the formation of a lumen.
7. Renal cancer develops from the epithelium, both of the pelvis and of the tubules.
8. In all specimens studied, the kidney in some portion showed an inflammatory reaction. The destruction of the renal substance varied in degree and was brought about by interstitial or parenchymatous changes or both; and suppuration was of frequent occurrence.
9. The epithelial lining of renal tubules may, under the influence of renal stone, (1) necrose, (2) form cysts, or (3) become malignant.
10. After having seen the gradual changes from normal tissue to inflammatory, from inflammatory to hyperplastic, and from hyperplastic to neoplastic, it appears probable that the chronic irritation brought on by the stones was the direct cause of the cancer.
11. In all the cases of renal cancer associated with renal stone, a large, light, fat-containing cell is found, sometimes singly, sometimes arranged in groups, and sometimes in definite columns. It has its origin in the tubules of the kidney. Further study will be made of this cell.
12. Of the total number of kidneys with cancer removed at the Mayo Clinic, 64+ per cent were associated with stones and 35+ per cent were without stones.

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## AN EXPERIMENTAL STUDY OF LAVAGE IN ACUTE CARBOLIC ACID POISONING.\*

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Acute poisoning with phenol, or carbolic acid, is one of the commonest forms of fatal poisoning met with in this country and, according to Blyth,<sup>1</sup> in England it occupies the highest place in the fatality list of all poisons.

Although phenol poisoning is now fortunately but rarely met with in surgical practice, the drug is still a favorite one among those who are bent on self-destruction and is often, also, swallowed accidentally for other medicines. Owing to its rapidly toxic action upon the central nervous system and the heart, phenol is one of the most quickly fatal poisons, and almost every medical man of experience has seen or heard of a man or a woman succumbing rapidly in some thirty minutes, sometimes less, after swallowing an ounce of pure carbolic acid. To save a patient, therefore, very prompt attention is required, and appropriate first aid is of vital importance.

Lavage of the stomach has for a long time been recommended in all cases of phenol poisoning, and for this purpose either plain water or watery solutions of various substances

have been employed. Numerous substances—albumen, syrup of lime, solutions of iodine or potassium permanganate, milk, and others—have been recommended for this purpose. Two drugs, however, in particular, have been used in this connection on seemingly rational grounds. These are alcohol and sodium sulphate.

The internal use of alcohol in carbolic-acid poisoning originated from a rather naive and, as we shall see later, fallacious deduction that, because alcohol is an excellent antidote for carbolic-acid burns of the skin, therefore it must be useful in the treatment of carbolic-acid burns of the stomach. This use of alcohol as an antidote in phenol poisoning was first brought before the medical profession by a certain Dr. Seneca D. Powell, of New York City, who was in the habit of demonstrating his theory by washing his hands in pure carbolic acid and then in alcohol, and even filling his mouth with pure acid and quickly rinsing it with 95 per cent alcohol without experiencing harmful results. From these experiments he drew the general conclusion that alcohol is an antidote to carbolic acid and suggested its internal use in cases of poisoning.<sup>2</sup> The first such use of alcohol in poisoning cases on record is

\* Read before The Johns Hopkins Hospital Medical Society, Nov. 16, 1914.



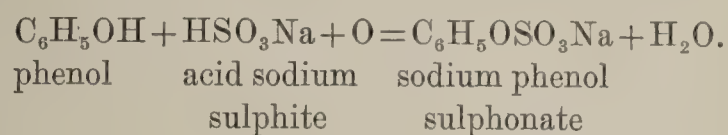
credited to Dr. J. D. Buchanan, who washed the stomach of a patient, who had taken one ounce of the acid, with two quarts of 95 per cent alcohol.<sup>3</sup> Since then a number of isolated cases thus treated are to be found in the literature, from which the most positive conclusions have been drawn. Thus, for example, Kelly<sup>4</sup> in 1899, after reporting one successful case, remarks that "alcohol is undoubtedly the best antidote for all cases of carbolic acid poisoning, and, indeed, is an absolute antidote." Phelps<sup>5</sup> states: "In cases of carbolic-acid poisoning, if immediately after the administration of the poison alcohol be thrown into the stomach the poisonous effects of the carbolic acid will be neutralized." Again, Pinkney,<sup>6</sup> after relating a fatal case, says: "The amount of carbolic acid left in the stomach and intestines when alcohol came in contact with it was rendered harmless, and the general action of the slowly absorbed poison was checked immediately."

The only really scientific attempt to determine the value of alcohol in this connection was made in 1906 by Clarke and Brown.<sup>7</sup> These authors collected and analyzed all the clinical cases available which had been treated with alcohol, and also made some experiments on animals. Their conclusions are, however, somewhat contradictory. On the one hand, from a study of the clinical cases, they conclude "there was no material difference in the mortality whether the stomach was washed with alcohol or with some other liquid, and the apparently greater constitutional symptoms when the drug was taken with alcohol than when taken clear or in water seemed to throw grave doubts on the antidotal power of alcohol." On the other hand, after their experimental work they conclude: "In cases of poisoning, lavage with alcohol is apparently an effective method of treatment," and "the procedure recommended is immediate abundant lavage with 10 per cent alcohol, followed by lavage with plain water, and stimulation as indicated."

It will thus be seen that the value of alcohol in carbolic-acid poisoning is still unsettled.

A very similar confusion as to its usefulness prevails regarding sodium sulphate. The introduction of this drug in the treatment of phenol poisoning goes back to the observations of Baumann in 1876.<sup>8</sup> Baumann painted the skin of a dog with phenol and at the same time fed the animal on sodium sulphate, and found paired sulphates in the urine. He, therefore, recommended the sulphates as direct chemical antidotes to carbolic acid. Cerna<sup>9</sup> and Cafrawy<sup>10</sup> each made experiments on animals, their observations apparently confirming this view, but their work is not regarded as convincing, as the doses of carbolic acid which they used were too small. Clinically, Sonenburg<sup>11</sup> found that the dark color of the urine and other symptoms rapidly disappeared after the administration of sodium sulphate. On the other hand, Küster<sup>12</sup> found that intravenous injections of sodium sulphate had little or no effect on phenol poisoning; and Tauber's careful work<sup>13</sup> threw still more doubt upon the subject. The latter observer studied the effect of subcutaneous and intravenous injections of sodium sulphate, pyrosulphate, ethylsulphate, sulphite, dithionate, and thiosulphate, in animals

poisoned with carbolic acid, and noted a neutralization or detoxification of the phenol only in the case of the sodium sulphite, from which it would seem that phenol does not combine with the sulphates as such in the body, but with organic sulphur compounds, which are in process of being oxidized to sulphuric acid, as illustrated by the following formula:



The use of the sulphite intravenously would hardly be suitable in clinical cases, nor would its employment even *per os* be devoid of danger. Sodium sulphate, however, has been employed in lavage, and various authors have reported recoveries after its administration. As an instance may be cited the case of Model.<sup>14</sup> A girl 9 years of age had swallowed a tablespoonful of carbolic acid on an empty stomach, and quickly became unconscious. Two hours later her stomach was washed out with a strong solution of Glauber's salts, and she recovered.

The present research was undertaken with the object of ascertaining the comparative advantages of various modes of lavage in phenol poisoning, and thus determining the most suitable and efficient method of rendering first aid in these unfortunate cases. Such a study was deemed particularly desirable for two reasons: firstly, because of the confusion and lack of agreement among various writers on the subject; and, secondly, because through the experimental work of Sollmann, Hanzlik and Pilcher<sup>15</sup> we have good reason to believe that lavage in these cases may really be of some benefit and not a hopeless procedure. These observers made quantitative studies on the gastro-intestinal absorption of drugs and found that "When phenol is placed in the alimentary canal the absorption is at first very rapid, but is quickly checked and soon practically arrested"; and "When phenol is placed in the stomach, only traces pass into the intestine; a large proportion could be removed by gastric lavage, even several hours after the phenol was taken."

I have introduced liquefied carbolic acid, both in concentrated solution and in various dilutions, through a stomach tube into the stomachs of various animals, and washed their stomachs out thoroughly at different periods of time after the appearance of the toxic symptoms. As is well known, the first symptoms of carbolic-acid poisoning in higher animals are weakness and a peculiar muscular tremor different from that produced by other convulsants, such as physostigmin and santonin<sup>16</sup>; these are quickly followed by clonic convulsions, collapse, coma and death. The animal suffers very little pain. In our experiments the animals were first anesthetized with ether, but as phenol, in the doses used, itself quickly paralyzes the central nervous system and the animals never show signs of pain, this preliminary anesthesia, for closer scientific observation, was dispensed with in some of the later experiments. This anesthetic action of carbolic acid is well known, and has also been confirmed in man. In the



human being convulsions are comparatively rarely seen, and when large quantities have been taken almost immediate unconsciousness may result.

#### ANIMALS STUDIED.

The animals most suitable for the study of lavage are cats and dogs. For further pharmacological analysis some experiments were made on frogs, rabbits, white mice and white rats. A large number of experiments were made. To give them all even in tabular form would require too much valuable space. Only a sufficient number of protocols is, therefore, given here to illustrate the salient features of the investigation.

For convenience of description the dosage of phenol in this paper is usually indicated in cubic centimeters of the official phenol liquefactum of the United States Pharmacopœia, or acidum carbolicum liquefactum of the British Pharmacopœia. Phenol, as is well known, consists of solid crystals, which readily take up 10 parts of water forming the liquid phenol. One cubic centimeter of this liquid is practically equivalent to 1 gram of phenol.

#### SUBSTANCES STUDIED.

Solutions or suspensions of various substances were tried in washing out the phenol from the stomach. Among these were egg albumen, alcohol, sodium sulphate, sodium sulphite, and syrup of lime. Of these albumen was found of very little value and sodium sulphite was too poisonous to be taken internally. Lime water and syrup of lime have been recommended by some authors in the hope that an insoluble combination might be formed in the stomach, but our experience with them was very unsatisfactory. My chief attention was therefore directed to the comparative study of the three reagents most used in phenol poisoning, namely, plain water, and aqueous solutions of alcohol and of sodium sulphate.

#### LETHAL DOSE.

Before attempting to save the animals by lavage, it was necessary to determine the smallest dose of the drug required to kill the animal in a short time. As even small doses of phenol through continual convulsions and exhaustion will kill an animal in a prolonged period of time, our experiments were directed to determining the smallest lethal dose, causing acute exitus in an hour or two. In this respect, a marked difference was found between the dog and cat. Though the symptoms and signs of poisoning are the same in both kinds of animal, cats were found much more susceptible to carbolic acid. The lethal dose for dogs was found to be about 0.5 cc. of the official phenol liquefactum per kilo. of weight; that for cats less than 0.1 cc. per kilo. of weight. These figures agree very well with those of Tollens<sup>17</sup> and other experimenters. As might have been expected, the presence of food in the stomach retards the absorption and binds some of the drug, so that a larger dose is required and the symptoms of poisoning appear later. The following protocols will serve to illustrate the rapidly fatal toxicity of carbolic acid:

EXP. 3. Oct. 29, 1913. Cat. Wt. 2 kgs. Stomach empty. Has not been fed since day before.

Introduced into stomach through rubber tube 0.15 cc. of acidum carbolicum liquefactum, mixed with water to make a 10 per cent solution.

Clonic convulsions appeared in 2½ minutes and death, from stoppage of heart and respiration simultaneously, one minute later.

EXP. 34. July 30, 1914. Male dog. Wt. 13 kgs. Stomach empty.

10.20 a. m., introduced 6.5 cc. of pure carbolic acid mixed with water to make a 10 per cent solution. Clonic convulsions set in 2½ minutes later.

10.40 Dog died while being put on table for lavage.

EXP. 1. Oct. 13, 1913. Cat. Wt. 3 kgs.

Introduced through stomach tube 1 cc. of pure carbolic acid diluted one-half with water.

2 minutes later, general clonic convulsions of body and jaws.

20 minutes later, continued convulsions; pulse 130 per minute, fairly strong.

30 minutes later, breathing shallow and very slow; pulse weak, 120 per minute.

60 minutes later, convulsions and retching movements.

96 minutes later, continued convulsions, coma, and very weak pulse, 120 per minute.

110 minutes later, heart irregular and can hardly be heard with stethoscope.

2 hours later, still in convulsions; bloody vomitus.

2½ hours later, convulsions weaker.

5 hours later, dead.

At autopsy, lungs very markedly congested, heart dilated, and stomach *full of food*.

It may be interesting in this connection to note the fatal dose of carbolic acid in man. Very small doses of carbolic acid taken internally have resulted fatally. Thus in one case, a girl, 24 years old, died shortly after taking 1.5 gm. of phenol.<sup>18</sup> In another case one drachm (4 cc.) proved fatal to a girl of 17 years.<sup>19</sup> Ordinarily the fatal dose, however, is much higher. Lewin<sup>20</sup> places it at from 8.5 to 60 gm. This corresponds with the ordinary doses taken for suicidal purposes in this country, which average about one ounce. If we reckon the average weight of man at about 70 kgs. it will be seen that the lethal dose per kilo. for man approaches very closely to that for the dog.

#### RESULTS OF LAVAGE IN CATS.

The success or failure of lavage in rescuing the animal was found to depend on the amount of phenol introduced, the time of lavage after the appearance of the toxic symptoms, and the solutions used.

In poisonings with small, though lethal, doses of carbolic acid, in which the stomach was washed immediately on the appearance of convulsions, that is, three to five minutes after ingestion of the drug, it was found that the animals could in most cases be saved by washing the stomach out thoroughly with either plain water or a concentrated solution of sodium sulphate. Lavage with solutions of alcohol was followed sometimes by recovery, but more often by death.

After larger doses of phenol *prompt* lavage with alcohol resulted almost invariably in death; washing the stomach with



plain water failed likewise to save the animal; but lavage with sodium sulphate was often attended with favorable results, and the animal either survived longer or completely recovered.

After *later* lavage, however, it was found that washing with alcohol or plain water was invariably followed by death, whereas lavage with sodium sulphate occasionally saved the animal. As cats are extremely susceptible to phenol poisoning, lavage could never be used to advantage later than 10 minutes after introduction of the poison into the system.

The following protocols will illustrate some of the above-mentioned results:

EXP. 2. Oct. 22, 1913. Cat. Wt. 2.5 kgs.

Introduced through stomach tube 0.5 cc. pure phenol liquefactum mixed with five times its volume of water. Stomach empty.

Convulsions appeared one minute later. Lavage with plain water 2 minutes later. Death in 5 minutes.

EXP. 12. Nov. 10, 1914. Cat. Wt. 3.2 kgs.

Introduced through stomach tube 3.2 cc. of 10 per cent carbolic acid solution. The animal had been fed a few hours previously. Convulsions began in 3 minutes.

Lavage with plain water one minute later. In 10 minutes the animal had recovered.

EXP. 6. Oct. 20, 1913. Cat. Wt. 1.5 kgs.

Introduced through stomach tube 1 cc. of pure carbolic acid mixed with an equal volume of water. The animal had been fed a short time previously.

Convulsions began in 2 minutes. Then immediate lavage was begun with 40 per cent alcohol followed by plain water. The animal died in 5 minutes.

EXP. 15. Nov. 12, 1914. Cat. Wt. 2.9 kgs.

Introduced through stomach tube 2.9 cc. of 10 per cent carbolic acid solution.

Convulsions began in 2½ minutes.

Lavage with 20 per cent alcohol 3 minutes later, then with water. Death occurred 5 minutes later through sudden stoppage of the heart.

EXP. 8. Oct. 12, 1913. Cat. Wt. 2.5 kgs.

Introduced 0.5 cc. of pure carbolic acid diluted with 10 times its volume of water. The stomach contained no food.

Convulsions appeared in 3 minutes.

Began washing with concentrated solution of sodium sulphate one minute later.

At the end of 10 minutes the heart and respiration were good. 20 minutes after poisoning, the animal recovered consciousness and cried.

30 minutes after poisoning the convulsions subsided, only muscular tremor being noted.

1 hour and 15 minutes later the cat lay quietly, drank water, and was in good condition.

EXP. 17. Nov. 10, 1913. Cat. Wt. 2.5

Introduced through stomach tube 1.25 cc. of 10 per cent carbolic acid.

Convulsions appeared in 2 minutes. After 5 minutes, lavage with sodium sulphate.

Heart stopped suddenly.

#### RESULTS OF LAVAGE IN DOGS.

Our experience with dogs was more promising than with cats. Whereas the latter are extremely susceptible to the toxic action of phenol, dogs are able to withstand larger

quantities of it and for a longer period of time. The results of the findings may be briefly summarized as follows:

By *immediate* lavage after introduction of lethal quantities of phenol it is possible to save the animals by washing, irrespective of the medium used, even though toxic symptoms are present.

After larger doses of the drug immediate lavage with sodium sulphate or with plain water may save the animal; washing with alcohol almost always results in death.

In *late* lavage (about 15 minutes after the introduction of the poison into the stomach) washing with sodium sulphate solution was found to give the best results; next in usefulness was plain water, whereas washing with alcohol resulted almost invariably fatally.

The following protocols will illustrate some of the findings:

EXP. 23. July 20, 1914. Dog. Wt. 5.4 kgs.

Introduced through stomach tube 5.4 cc. of pure carbolic acid mixed with 10 parts of water.

Clonic convulsions began in 3 minutes. Copious lavage with 2 litres of plain water was begun 2 minutes later and continued until the drug could not be smelled in the washings.

Taken off the table unconscious, but with heart and respiration in good condition. Recovery in 1 hour.

Here we see recovery after a large dose of phenol, following *immediate* lavage with water.

EXP. 30. July 30, 1914. Dog. Wt. 10.5 kgs.

10.10. Introduced through stomach tube 5.25 cc. of pure carbolic acid in 10 parts of water.

Clonic convulsions began in 2 minutes.

10.30 a. m. Began lavage with plain water, 3 litres.

11.15 a. m. Convulsions much less violent, but still unconscious.

2.00 p. m. Convulsions continue.

3.30 p. m. Still unconscious.

July 31, 9 a. m. Found dead.

Here we see that washing with water, begun 20 minutes after ingestion of the poison, was of no avail.

EXP. 20. July 22, 1914. Large dog. Wt. 11 kgs.

3.38 p. m. Introduced 11 cc. of pure carbolic acid mixed with 10 times its volume of water.

2.55 p. m. Dog shows a slight tremor, but no convulsions. No vomiting.

2.58 p. m. Introduced 11 cc. more of pure carbolic acid in 100 cc. of water.

3.20 p. m. Dog sick, lying down, half unconscious.

3.23 p. m. Began washing with concentrated solution of sodium sulphate. Some food was found in stomach.

3.34 p. m. Lavage stopped. Dog taken off table in good condition. Was found in perfect health next morning.

In this case recovery took place after lavage with sodium sulphate begun 45 minutes after the first dose of the poison, and after an enormous total quantity of carbolic acid, 22 cc. in all. The presence of food in the stomach undoubtedly favored the successful outcome.

EXP. 25. July 23, 1914. Dog. Wt. 6 kgs. In poor health. Suffering from distemper.

Introduced through stomach tube 3 cc. pure carbolic acid with 5 parts of water.

Convulsions began 3 minutes later; unconscious.



10 minutes later lavage with sodium sulphate solution. Recovery, but death a day later.

Here we find recovery, at least temporary, in a previously sick dog, after lavage with sodium sulphate solution.

EXP. 36. July, 1914. Dog. Wt. 7 kgs.

1.24 p. m. Gave 3.5 cc. pure carbolic acid in 10 parts of water.

1.25 p. m. Clonic convulsions.

1.40 p. m. Began washing with 15 per cent alcohol.

1.41 p. m. Dog died on the table. Further washing revealed food in the stomach.

Here we had sudden death while washing with alcohol, after a not excessive dose of phenol and with the stomach full of food. Compare this experiment with Exp. 20, described above.

EXP. 40. July, 1914. Dog. Wt. 7 kgs.

Introduced 7 cc. of pure carbolic acid mixed with 10 parts of water.

Clonic convulsions set in 2 minutes later.

Immediately after lavage was begun with 20 per cent alcohol, followed by plain water.

The respirations stopped suddenly and the heart beat became imperceptible.

Gave artificial respiration and massage of heart.

Animal began to breathe again 5 minutes later.

Taken off table in moribund condition.

Next day signs of recovery, but death later.

#### ANALYSIS AND DISCUSSION.

From the above protocols it will be seen that introduction of phenol into the stomach of cats and dogs, in sufficient quantity will without a therapeutic procedure invariably produce death; but that the animal can often be saved by thorough lavage of the stomach. Of the three reagents used for this purpose and chiefly studied in this connection, sodium sulphate was found to be the most efficient, next in order being plain water. Alcohol was found to be distinctly deleterious, and often appeared to hasten a fatal issue. The chances of rescuing an animal depend firstly on the dose of poison swallowed or introduced into the stomach; secondly, on the promptness with which the lavage is begun, and, thirdly, on the solution used in washing the stomach. The earlier the lavage is begun the greater the chances of recovery, even though a large quantity of the poison has been taken. The presence of food in the stomach greatly increases the chances of recovery. In my experiments I have purposely refrained from any other measures in resuscitating the animal except artificial respiration, massaging the precordium, and keeping the animal warm; but the judicious use of stimulants would seem to be indicated, although in the few experiments in which I tried them no striking effects were noted. For the use of emetics recommended by some authors, there seems to be no rational ground.

If we compare the lethal dose of phenol per kilo. of a dog with the fatal dose given by most authors for man, we shall see that the toxicity of phenol for the two is about the same. We have reason, therefore, to expect that the same measures may be applicable in cases of carbolic-acid poisoning in the

human being, and indeed, as already mentioned, some clinical reports of lavage with sodium sulphate appear to sustain this view.

The action of sodium sulphate, however, in this connection is probably not a chemical one, as has been conclusively proved by Tauber. The action must probably be due to the hindering of absorption and possibly also to purgation of the animal. For the same reasons magnesium sulphate could be used, but its use is to be discouraged on account of the possibly depressing effect of the magnesium ions, in case of their absorption.

#### ON THE RÔLE OF ALCOHOL IN PHENOL POISONING.

The unfavorable action of alcohol in cases of carbolic-acid poisoning just noted seems to be contrary to the popular experience with this form of poisoning. Most of us have seen or heard of cases in which whiskey had apparently saved a man from death by carbolic acid. As an example, I will quote a news item, which I have very recently cut out of a paper, and which will serve as a good illustration of what I mean:

Robert C., 24 years old, because he could not find work, drank carbolic acid here last night. C. first drank whiskey to stupefy himself before taking the poison. The whiskey in a measure counteracted the effect of the deadly drug. He was found by his wife lying in bed writhing in agony. C. was quickly rushed to the hospital, where he is still suffering.

Such cases are not fakes. I have seen them myself. How can we reconcile them with our experimental data? To clear up the problem, the idea suggested itself to try the following experiments:

EXP. 47. July 21, 1914. Kitten A. Wt. 0.7 kg.

Introduced into stomach 1 cc. of 95 per cent alcohol diluted with 10 parts of water. 15 minutes later introduced 1 cc. more of 95 per cent alcohol diluted with 10 parts of water. 1 hour later, the animal was found to be thoroughly drunk. It could not stand on its feet, and was drowsy. The heart and respiration, however, were regular and good. 0.7 cc. of a 10 per cent solution of carbolic acid was then introduced into stomach.

Convulsions appeared in 5 minutes. The animal's stomach was then washed with 500 cc. of plain water. The pulse and respiration continued good and the animal made a rapid and perfect recovery. It was well and was used for another experiment the next day.

EXP. 48. July 21, 1914. Kitten B. Wt. 1.2 kgs.

Introduced 1.2 cc. of 10 per cent carbolic acid into the stomach. Clonic convulsions set in 2 minutes later. Washed immediately with 500 cc. of 15 per cent alcohol, followed immediately by plain water. Heart and respiration stop and animal succumbs in a few minutes.

EXP. 49. July 22, 1914. Kitten C. Wt. 0.8 kg. Washed the stomach with 500 cc. of 15 per cent alcohol, followed immediately by 500 cc. of plain water.

No convulsions noted. Animal goes to sleep; wakes up 2 hours later and is perfectly normal.

On comparing these three experiments it will be seen that Kitten B, which received 0.1 cc. per kg. of liquid phenol, developed convulsions in 2 minutes, and succumbed after prompt lavage with alcohol, followed by water.

Kitten A, which was previously thoroughly intoxicated with alcohol and then received a similar dose of phenol, de-



veloped convulsions later, that is, 5 minutes after the introduction of the poison; but its heart and respirations continued good, and it recovered after lavage with plain water.

That washing with alcohol alone will not kill an animal is shown by the control experiment on Kitten C.

An exactly parallel series of experiments with exactly similar results was made on dogs, as shown by the following protocols:

EXP. 43. July 27, 1914. Dog A. Wt. 11 kgs. In good condition.

10.00 a. m. Given 20 cc. of 95 per cent alcohol diluted with 5 parts of water.

2.00 p. m. Thoroughly drunk and drowsy; salivated.

2.20 p. m. Introduced 5.5 cc. pure carbolic acid in 10 times its volume of water.

2.25 p. m. Slight tremor and weak convulsions.

2.35 p. m. Washed stomach thoroughly with water until smell of phenol could not be detected. Pulse and respirations good.

Taken off the table unconscious and trembling, but in fair condition. Recovery next day.

EXP. 37. July 27, 1914. Dog B. Wt. 8 kgs. In good condition.

2.25 p. m. Introduced 4 cc. of pure carbolic acid in 10 times its volume of water.

2.28 p. m. Convulsions appear.

2.40 p. m. Washed stomach with 1 litre of 15 per cent alcohol, followed immediately by water.

Heart and respirations stop suddenly. Dog dies on table.

EXP. 44. July 27, 1914. Dog C. Wt. 7 kgs. In good condition.

Washed stomach with 1 litre of 20 per cent alcohol, followed immediately by 1 litre of water. Taken off table conscious and in good condition. Next day, normal.

The following protocol shows that in a previously alcoholized dog recovery is possible even after an enormous dose of carbolic acid:

EXP. 46. July, 1914. Dog. Wt. 5.4 kgs.

Given 10 cc. of 95 per cent alcohol in 10 parts of water. One hour later 10 cc. more of 95 per cent alcohol in 10 parts of water. When the dog was thoroughly narcotized, one hour later, 5.4 cc. of pure carbolic acid, *i. e.*, 1 cc. per kg., or twice the fatal dose, were introduced into the stomach, mixed with 5 parts of water.

Slight convulsions set in in 4 minutes. Lavage with plain water was then begun. The heart and respirations did not fail throughout the operation. The dog was taken off the table unconscious, and showed a tremor but no violent convulsions. One hour later the animal was seen walking around and in pretty good condition, no worse for his experience.

These experiments, as well as a sufficient number of others which I need not give here in detail, bring out the very interesting fact that there was a very great difference in animals which had previously received alcohol and subsequently phenol, and those in which the administration of alcohol was subsequent to or simultaneous with that of the phenol. Hence we may conclude that animals which have been previously poisoned with alcohol are able better to withstand the action of phenol. What the explanation of this curious phenomenon is is not quite clear, but the result is probably due to the greater affinity of the alcohol for the nerve cells, which prevents the phenol from getting hold of them. The effect of alcohol *after* the ingestion of phenol is simply to promote still further absorption of the acid as it acts as an excellent solvent for phenol. Dr. Turner, of the

pharmacological laboratory, suggests that the difference of the effect in the two cases may further be explained on the theory of surface tension.

It was interesting to find that the same conditions hold good after the *subcutaneous* administration of alcohol and phenol.

For this purpose I utilized smaller animals, namely, white rats and kittens. The following protocols will illustrate the findings:

EXP. 57. Oct. 24, 1914. White rat. Wt. 90 gms.

2.00 p. m. Injected under skin 25 mgs. of phenol in 5 per cent solution.

2.04 p. m. Tremor noted.

2.06 p. m. Clonic convulsions begin.

2.25 p. m. Very rapid convulsions, too rapid to count.

2.30 p. m. Convulsions 168 per minute.

3.00 p. m. Same.

4.55 p. m. Death.

EXP. 58. Oct. 24, 1914. White rat. Wt. 65 gms.

2.02 p. m. Injected under skin 2 cc. of 10 per cent alcohol.

2.20 p. m. Animal distinctly drunk but conscious.

2.21 p. m. Injected 50 gms. of phenol in 5 per cent solution.

2.26 p. m. Convulsions begin but are not as rapid as in other animal.

2.30 p. m. Convulsions 140 per minute.

3.00 p. m. Convulsions slower.

6.00 p. m. Still alive.

Found dead next day.

EXP. 51. Oct. 20, 1914. Kitten. Wt. 0.8 kg.

1.25 p. m. Injected 2 cc. of 5 per cent carbolic acid.

1.26 p. m. Tremor noticeable.

1.27 p. m. Clonic convulsions.

1.38 p. m. Coma and rapid convulsions.

1.45 p. m. Same.

2.00 p. m. Same.

2.45 p. m. Same. Injected 2 cc. more of 5 per cent carbolic acid.

3.30 p. m. Very violent convulsions.

6.00 p. m. Exhausted.

9.00 p. m. Death.

EXP. 52. Oct. 20, 1914. Kitten. Wt. 0.7 kg.

12 m. Given 3 cc. of 95 per cent alcohol in water.

1.15 p. m. Animal distinctly drunk.

1.25 p. m. Injected 2 cc. of 5 per cent carbolic acid.

1.27 p. m. No convulsions.

1.38 p. m. Slight tremor but no convulsions.

1.45 p. m. Tremor but no convulsions.

2.00 p. m. Slight convulsions noted.

2.30 p. m. Same.

2.45 p. m. Injected 2 cc. more of 5 per cent carbolic acid.

3.30 p. m. Very little change.

6.00 p. m. Convulsions getting stronger.

10 p. m. Convulsions continued.

Found dead next day.

It can be pretty safely assumed that the above experiments furnish an explanation for the conflicting opinions in respect to the value of alcohol in carbolic-acid poisoning. A previously drunken person will probably withstand the ravages of phenol better, whereas one that takes carbolic acid mixed in alcohol, or victims of phenol poisoning washed or doused with alcohol for therapeutic purposes, are more liable to perish. Thus it is interesting to note that of ten cases (mentioned by Falck<sup>21</sup>) of carbolic-acid poisoning where the victims



drank carbolic acid in various alcoholic drinks, such as schnapps, brandy, rum, or beer, 9 of the 10 succumbed; whereas of 17 persons who drank carbolic acid simply by mistake, only 13 died.

The practical importance of this fact cannot be overestimated, for on the one hand we frequently read news items, such as the one quoted above, and on the other we still find standard works on toxicology which advise the administration of alcohol in carbolic-acid poisoning. Thus one of the most popular American text-books on Legal Medicine and Toxicology says:<sup>22</sup> "Alcohol is the best antidote. When the poison has been swallowed whiskey may be taken with advantage." And in one of the standard American reference works on toxicology we read the following:<sup>23</sup> "It seems very probable that the best method of treating a case of carbolic-acid poisoning would be to administer alcohol, provided the stomach be washed out immediately afterward." It was therefore with great pleasure that I read in another recent text-book by Holland<sup>24</sup> the statement based on purely chemical grounds: "Dependence should not be placed on alcohol as an antidote."

#### SUMMARY.

1. The efficiency of lavage in phenol poisoning depends on the quantity of poison taken, on the time after poisoning that the lavage is begun, and on the solution used for washing the stomach.

2. A strong solution of sodium sulphate appears to be the most useful for the purpose; next in efficiency comes plain water.

3. The influence of alcohol in phenol poisoning depends on the time of its administration. An animal that is previously

intoxicated with alcohol can withstand better the effects of phenol taken afterwards. On the other hand, alcohol administered to an animal after poisoning with phenol will aggravate the symptoms and hasten death.

4. The use of alcohol in carbolic-acid poisoning should therefore be strongly discouraged.

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## THE BEGINNINGS OF MEDICINE IN THE MIDDLE WEST.\*

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The story of the birth and development of medical thought and practice in the interior valley of North America is closely interwoven with the inception and growth of Western education and culture. The men who were the pioneers of medical art and science in the Western country were, almost without exception, men of affairs who stood in the foreground of public life and crystallized the genius and the ideals of their time and their country in a characteristic manner. They were not only the makers of medicine in the West, but contributed in no inconsiderable degree to the social and educational history of our republic. Whatever there is of great and momentous power in American history, is in many instances closely affiliated with the names of illustrious physicians who were the standard-bearers of civilization in those early days, and not only helped to mould the character of our profession, but were the leaders in the eternal struggle for the altruistic ideals of humanity.

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The early beginnings of medicine in the Middle West were coincident with the dawn of the nineteenth century. The century was only nine years old when an event of the greatest historic moment established Western Medicine as a distinct chapter in the annals of medicine generally. In 1809 Ephraim McDowell made his memorable contribution to the possibilities of operative surgery. It was an event of far more than ordinary importance and, considering all the circumstances, may be accepted as a distinctly Western achievement. McDowell came to the pioneer settlement of Danville, Ky., when he was 13 years of age. He developed into a Western doctor of the early times—shrewd, resourceful, dignified, truthful, and replete with the academic flavor which his training under John Bell, of Edinboro, had given him. McDowell's ovariectomy in 1809 undoubtedly meant a great display of courage as well as of anatomic and pathologic knowledge. Some say it was one of the greatest feats in the history of surgical art. Inasmuch as it paved the way for the entire subject of abdominal surgery in the treatment of diseases of women,



McDowell's operation is not likely to lose much of its glamour by historic or any other kind of analysis. But this is not the point that is of consequence to us on this particular occasion. I want to emphasize to you the fact that Ephraim McDowell was a Western doctor and that his historic operation in 1809 was the first awakening of scientific medical thought on the other side of the Alleghany Mountains. The name of McDowell has such a familiar ring and the history of his great work has been told so well and so often that I can assume familiarity with it here, where the work, begun by that great pioneer-surgeon, has been evolved and developed as much as, if not more than, anywhere on this continent. I could not add any new immortality to the name of the father of ovariectomy by again telling the story of his work.

What preceded him and his work in the newly colonized West, say after 1785, was of no characteristic import. The pioneer-settlers were the carriers of civilization and many doctors, mostly from the East and perhaps officially attached to some of the military posts in the West, practiced medicine among the settlers. Most of them were not graduate physicians. There were no schools of medicine in the new territory and only one in the East. A good type of the itinerant Western doctor of early times was Peter Smith, originally a New Jersey man, who went to Virginia with a B. A. from Princeton, and began to preach the gospel to the new colonists. He lingered for a time in Virginia, then in the Carolinas and finally settled in Georgia as an old-fashioned Baptist minister. Being a strong anti-slavery man, even in those early days, he found himself in continuous trouble with his neighbors, who were all slave-holders. He decided to leave and began to meander through the country with his family. His wife sat on a big horse; the two smallest children slept in baskets hung to the horns of the saddle, the other children, thirteen in all, walking along on either side of the horse. Smith traversed Georgia, Tennessee and Kentucky in this fashion. He was disgusted with the slavery he found everywhere and decided to leave the South and its scorpions, head-ticks, bad whiskey and slaves, as he expressed himself. He came to Cincinnati about 1794 and preached in the old Baptist church on Duck creek, near Cincinnati. After some years he moved to Donnell's Creek, Ohio, and became a farmer. He died here in 1816.

Smith was the son of a physician and in traveling from place to place, picked up bits of medical knowledge. He was particularly interested in the medical notions of the Indians, and eventually expanded his work by becoming a healer of the body in addition to being a minister of the soul. In 1812, while engaged in missionary work in Cincinnati, he published a book on his methods of practice under the title of "The Indian Doctor's Dispensatory." This book, written by this picturesque itinerant doctor, is the first book on medicine published in the West. It is a curious publication, containing crude and strange medical superstitions and vagaries, and, with it all, much knowledge of the pathology of diseases and the physiological action of remedies. Smith is a strong advocate of sunlight, fresh air and water and a great believer in

the curative properties of the herbs used by the Indians. It is interesting to know that Rafinesque, who wrote on American plants many years later, quotes Smith very liberally and attaches much importance to his views. There are not more than three copies of Peter Smith's book still in existence. The Lloyd Library, of Cincinnati, has recently published it for the benefit of the many who are interested in the medical history of the West. Smith's Dispensatory was published in 1812. There was at that time very little of American medical literature to be found anywhere. When Smith's book appeared in Cincinnati not more than a dozen books on medicine had been written by Americans. Dorsey's Surgery and Wistar's Anatomy, at one time the most popular American books on their respective subjects, had not yet made their appearance. Peter Smith must have been a man of close observation and great originality, judging by the character of his work, no less than by the mere fact of publishing a book on medicine at a time when he could not help being original. Thus, he is a noteworthy character in American medicine and is entitled to a more respectable position in our history than has thus far been accorded to him. As I have stated, he was an herb-doctor or botanical practitioner. Men of this type, as you know, made a good deal of noise one hundred years ago. Peter Smith undoubtedly was one of the most original and interesting characters among these exotic products of the early times. I regret that I cannot show you a likeness of Peter Smith, the Indian doctor. There is no picture of him extant. The burial-place of this quaint and original pioneer is in a pitiful state of neglect. I have recently tried to interest the profession of Ohio in the memory of Peter Smith. We hope to soon be able to place a suitable memorial tablet on his grave to remind the present generation of the first medical author in the history of the West.

The events of the formative period of medicine in the West can be conveniently grouped around the gigantic figures of three men who loomed up approximately at the same time and influenced the development of medicine in a very direct and characteristic manner. One of them I have already mentioned. He was Ephraim McDowell, of Danville, Ky., whose ovariectomy in 1809 opened a new chapter in surgery and incidentally inaugurated the history of medicine in the West. McDowell did a great deal of creditable work and, while he was not connected with any of the early Western schools of medicine, trained and educated a number of young men who became great medical teachers and leaders of the profession in different parts of the country. One of his assistants, Alban Goldsmith, was one of the pioneers of genito-urinary surgery in this country and is remembered as professor of surgery at the New York College of Physicians and Surgeons. He was born and bred in Louisville, and owed his New York appointment to his great surgical ability. He witnessed McDowell's first operation and repeated the operation successfully on a number of occasions. McDowell died in 1830. His operation fell into disrepute after his death and the fruits of his labors would have been lost if it had not been for the work done by Alexander Dunlap, of Springfield, Ohio, who,



twelve years after the master's death, performed the classical ovariectomy of McDowell and precipitated an unparalleled avalanche of condemnation among the profession. Dunlap stuck to his post and convinced the profession by hundreds of good results that McDowell had really been a pathfinder in the interests of the human race. That McDowell's name and work were saved, we owe to the heroism and matchless professional ability of Dunlap and of his distinguished Eastern collaborator, Washington Atlee, of Philadelphia, whose name is likewise linked to that of the great Danville surgeon for all time to come.

I stated that the early medical history of the West was grouped around the heroic figures of three great men. McDowell, being the center of his own special activity, naturally remains in a class by himself. The other two men worked in the interests of medical education and became leaders of the profession along different lines. These two men, whose gigantic figures loom up in silent and solemn grandeur at the very inception of the story of Western civilization, seem larger and more imposing after the elapse of nearly a century and have long become landmarks, not only in the West, but in the United States, being among the most distinguished characters in the annals of medicine in America. One of them is Benjamin Winslow Dudley, the founder of the medical department of Transylvania University in Lexington, Ky.; the other is Daniel Drake, that wonderfully versatile and brilliant man who established the Medical College of Ohio in Cincinnati in 1819. The life work of these two eminent medical educators, more especially that of Drake, forms one of the brightest pages in the history of American medicine and was of incalculable service to the cause of civilization in that unexplored territory which, a century ago, was one vast empire of barbarism.

Benjamin Winslow Dudley, the father of the medical school in Lexington, Ky., was born in Virginia in 1785, but came to the pioneer town of Lexington when he was only one year old. Here he remained, lived, worked and died at the ripe old age of 85 years. He studied medicine at the medical department of the University of Pennsylvania. Young Dudley was an impressionable and ambitious student who drew no end of inspiration from the teaching of the famous men who composed the Philadelphia faculty. He graduated in 1806 and hastened back to Lexington to offer his friends and neighbors his stock of newly acquired knowledge. His ambition was to be a surgeon, but he waited in vain for patients who were willing to let him try his surgical skill on them. Dudley was poor and found himself compelled to adopt some method of keeping the wolf from the door. He purchased a flatboat, loaded it with produce, headed it for New Orleans, and floated down the Kentucky, the Ohio and Mississippi rivers to the desired port. He invested the proceeds of his cargo in flour. This he billed to Gibraltar, which he reached some time in 1810; there and at Lisbon he disposed of it with large profits. The liberal supply of filthy lucre in his pocket reawakened his medical ambition. He went to Paris and London and sat at the feet of the great masters of surgery. With new hopes and greater ambition than ever he returned to Lexington, where a disas-

trous epidemic of malignant typhus was raging. His European prestige proved to be quite a drawing card. Everybody wanted to be treated by the man who had studied in Paris and London. Thus Dudley in a few years became a famous physician and surgeon. In 1817 the trustees of Transylvania University in Lexington conceived the idea of adding a medical department to their institution and drew Dudley into their confidence. The word "Transylvania," as you may remember, was the original name of the colony which eventually developed into the state of Kentucky. When, in 1770, the charter for a seminary in Lexington "for the teaching of the higher branches of learning" was granted, it was decided to perpetuate the historic name by calling the new school "Transylvania Seminary," and afterwards "Transylvania University." Dr. Dudley was made the head of the medical department and at once proceeded to organize a faculty. The rise of this school, the first medical school in the West, was most auspicious. Lexington was noted for its culture and urbanity. It had 8,000 inhabitants, among them some wealthy people who, in addition to their shekels, had plenty of local patriotism to help the town along. Lexington was generally called the "Athens of the West," and nobody questioned its ultimate supremacy as the leading city in the Ohio Valley. Cincinnati at that time had 10,000 inhabitants, mostly workingmen, who had collected from all parts of this country and Europe and, of course, could not cope with their neighbors in Lexington, either in wealth or education. Compared to Cincinnati, a typical Western pioneer town, Lexington, with its wealth and fine colonial mansions, appeared like a metropolis. Yet, Cincinnati began to be well known in many places. A little pamphlet had appeared in 1810 which gave much information about the town and proved to be a mighty effective advertisement, especially in the East, where the pamphlet was eagerly read by people who intended to try their fortunes in the West. In 1815 a pretentious little volume appeared which gave still more definite information about Cincinnati, its topography, climate and municipal and civic possibilities. This book, called "Picture of Cincinnati", found its way to Europe, where parts of it were translated and published for the benefit of prospective emigrants. The author of the aforesaid pamphlet, as well as of the "Picture of Cincinnati," was a young physician whose name I have already mentioned. He was destined to become one of the greatest figures in American medicine and cannot inappropriately be called the Father of Western Medicine, namely, Daniel Drake. When Dudley was casting about for material to organize the Transylvania medical faculty he thought of Drake and offered him a professorship in his school. To be a professor in a medical school in the West was such a novel distinction that Drake did not hesitate for a moment to accept the offer. Before saying anything more about Dudley and his new school at Lexington, it seems proper to pause for a few moments and think of Drake, who, aside from his medical achievements, is the one really great character whose name is associated with the advance of civilization in the Ohio Valley and in the upbuilding of the entire West.

Drake and Dudley were born in the same year, 1785. Drake



was born in New Jersey and was about two years old when his father came West to locate near Maysville, Ky. Here young Drake was reared amid scarcity of money, but wealth of virtue, until he was 15 years of age, when his father arranged to send him to Cincinnati to study medicine under a typical doctor of colonial times, Dr. William Goforth. In 1805 Dr. Goforth made Drake a full-fledged doctor of medicine by granting him a diploma, the first diploma received by a medical student in the West. Later on Drake took a course in the medical department of the University of Pennsylvania and received the degree of doctor of medicine. In 1817 Drake left Cincinnati and went to Lexington as a member of the medical faculty of Transylvania University. Incidentally let me call attention to that splendid historical book, "Pioneer Life in Kentucky," in which Drake described his early childhood in the Blue Grass State. It is a book which everyone who is interested in the history of the West should read.

In connection with the early history of Cincinnati it is of interest to know that the two names of the town, namely, Losantiville and Cincinnati, were suggested by two men who were closely related to the medical profession. John Filson, who invented the first name of the town, namely, Losantiville, was a medical student and intended to locate as a physician in Lexington, Ky. "L" is the first letter of the word "Licking," the name of a Kentucky river, "anti" means opposite, "os" mouth and "ville" town. Thus Losantiville means "the town opposite the mouth of the Licking." Unfortunately Filson's career came to an untimely end before he had a chance to carry out his plans. The name of "Cincinnati" was the suggestion of General Arthur St. Clair. He wanted to thus honor the patriotic order of the "Cincinnati," of which he was a zealous member. Before the fortunes of war tempted him to become a soldier, he had studied medicine for one year in London under John Hunter.

The story of the medical department of the Transylvania University, especially the first decade of the school, presents a composite product of every phase of human emotion from the heroically sublime to the grotesquely ridiculous. It reads like an epic poem when the achievements of the really great men are referred to, who composed the faculty, beginning in 1817. Dudley was a tremendously able man, but he was intensely human. This fact injects much pathos and still more humor into the narrative. Thundering Jove was not a greater autocrat in the affairs of Olympus than Dudley was in the management of the Transylvania school. He was a giant in stature, had an awful temper, and when aroused, used language in the faculty room that laid no claim to elegance, while its force could not possibly be questioned. He was fond of emphasizing his remarks with his fist, which he would use with telling effect on the faculty table. Some of the professors were Kentuckians who did not take kindly to this mode of argumentation. The result not infrequently would be a fist-cuff engagement in which Dudley usually held his own. He used surgical instruments with consummate skill, but in true Kentucky style he was also very handy with a gun. One of the distinguished professors associated with Dudley was Wm.

H. Richardson, a typical Kentuckian, who came from an excellent family and was a very scholarly man. During one of the faculty meetings Richardson criticized some suggestion which Dudley had made. Dudley told him that if he did not keep his mouth shut he would shoot his —— head off. Richardson told him he would meet him at any time and accordingly a duel was arranged. The two gentlemen shot at the same moment. Richardson's bullet went astray, while Dudley's bullet struck Richardson in the leg, severing the femoral artery. Richardson would have bled to death if Dudley had not come to the rescue by ligating the artery. After the operation the two antagonists shook hands and were good friends ever after. In spite of this and similar occurrences, the medical school of Transylvania flourished and was for fully three decades one of the great American colleges of medicine. In 1826 the class numbered 235 students. Among the professors were some of the most distinguished medical men of their time. Dudley was a tower of strength. In spite of his erratic manner, he enjoyed the respect of his colleagues on account of his great ability as a surgeon. He performed more than 600 lithotomies with a mortality of only 4 per cent; and all this before the days of anesthesia and surgical cleanliness. This record alone stamps him as one of the immortals in the history of surgery. Another strong man of the faculty was Charles Caldwell, who was a wonderfully productive writer and was thought to be one of the (if not the) most learned American physicians of his time. His clever speculations on phrenology won him many admirers at that time and make good reading even to-day. Then there was Charles Wilkins Short, who had a national reputation as a botanist, and who is still remembered because some American plants bear his name. There were many other distinguished medical teachers connected with Transylvania. In 1839 the city of Lexington erected a special building for the medical school. About 1860 the medical department of Transylvania was abandoned. During its brilliant career more than 2000 American physicians had received their degree at the old school. The grim old warrior who had founded it, outlived it by ten years. He died in 1870.

During the thirties some of the medical professors of Transylvania seceded and joined the Louisville Medical Institute, which, after 1840, rose to great prominence. Daniel Drake taught at this school from 1840 to 1850. Samuel D. Gross, who afterwards rose to one of the most exalted stations in American medicine as professor of surgery in Jefferson Medical College of Philadelphia, was also connected with the school for a number of years. Lunsford P. Yandell, the professor of chemistry, had a great reputation in his day. This school was the prolific mother of a number of small medical colleges in Louisville that came, saw, and were finally absorbed into the medical department of the University of Louisville.

I mentioned the fact that Daniel Drake was one of the early professors in the Transylvania school. He remained just one year. One season with Dudley was all he could stand. Drake returned to Cincinnati in 1848 and at once got busy planning a medical college in Cincinnati. The result of his



activity was the Medical College of Ohio, which began a most tempestuous career in 1819. Within two years after the college had sprung into existence, Drake was expelled by his own faculty. The faculty consisted of Drake, Jesse Smith, professor of surgery, and Elijah Slack, the president of the old Cincinnati College, who taught chemistry. These three men were their own trustees and when trouble arose about some minor matters, Smith and Slack decided to expel Drake, which was accordingly done. Drake described this serio-comic episode in a pamphlet entitled "The Rise and Fall of the Medical College of Ohio." The pamphlet is a classic of its kind and shows the versatile Drake in a new rôle, that of a delightfully keen humorist. No physician who is interested in the medical history of the West should forego the pleasure of reading this unique document. I would not be doing my subject justice if I did not by way of a short quotation give you an idea of Drake's delicious humor. Drake tells the story of his expulsion in the following manner:

At 8 o'clock we met according to a previous agreement, and transacted some financial business. A profound silence ensued, our dim taper shed a blue light over the lurid faces of the plotters, and everything seemed ominous of an approaching revolution. On trying occasions Doctor Smith is said to be subject to a disease not unlike St. Vitus' dance, and on this occasion he did not wholly escape. Wan and trembling, he raised himself (with the exception of his eyes) and in lugubrious accents said, "Mr. President, in the resolution I am about to offer, I am influenced by no private feelings, but solely by a reference to the public good." He then read as follows: "Voted that Daniel Drake, M. D., be dismissed from the Medical College of Ohio." The portentous stillness recurred, and was not interrupted till I reminded the gentlemen of their designs. Mr. Slack, who is blessed with stronger nerves than his master, then rose, and adjusting himself to a firmer balance, put on a proper sanctimony and bewailingly ejaculated: "I second the motion." The crisis had now manifestly come; and, learning by inquiry that the gentlemen were ready to meet it, I put the question, which carried, in the classical language of Doctor Smith, "*nemo contradicente*." I could not do more than tender them a vote of thanks, nor less than withdraw, and, performing both, the doctor politely lit me downstairs."

After his expulsion Drake spent most of his time getting even. In 1831 the trustees of Miami University, of Oxford, Ohio, arranged with Drake to open a medical department in Cincinnati. Drake brought some excellent talent to Cincinnati, mainly from the East. The most distinguished medical teacher who was given a chair in the prospective medical department of Miami University was John Eberle, who came from Hagerstown, Md., and was lecturing at Jefferson Medical College when Drake asked him to come West. A very promising young man was Jas. Staughton of Washington, D. C., who was a graduate of the University of Pennsylvania and had spent two years in Europe studying under famous English and French surgeons. Upon his return he taught surgery at the Medical Department of Columbian College, of Washington, D. C., and attracted a great deal of attention as an eloquent and resourceful teacher. When Drake invited him to come to Cincinnati, he at once acceded and became the professor of surgery in the Medical College of Ohio. He died of cholera in 1833. He wrote two monographs possessing great merit,

one on "The Life and Services of Ambroise Paré," the other on "The History of Lithotomy."

Of the Eastern men who in the early days had come West to share in the work of establishing the science and profession of medicine, no one occupied a more honorable position East or West than John D. Godman, who was a native of Annapolis, Md., and was a graduate of the University of Maryland. He became the leading American anatomist of his time. Like Bichat of France, he died young, but his name will live as long as the cause to which he gave his efforts is not forgotten. Godman remained in Cincinnati but one year. He was a lover of peace and not a well man. He was, therefore, hardly prepared to prosper amid the stress and strife of the early existence of the Medical College of Ohio. While in Cincinnati he published the "Western Quarterly Reporter of Medical, Surgical and Natural Science," the first medical journal in the West. Godman, as you know, became professor of anatomy in Rutgers Medical College after he left Cincinnati. He died at the age of 36, young in years but old and mature in scholarship and intrinsic value and quality of creative activity. Another man who was a teacher in the Medical College of Ohio in the early days was Benjamin S. Bohrer, who came from Washington, D. C., and after a turbulent experience in Cincinnati, returned to his native town, where he rose to great distinction as a learned and cultured member of the profession. A noteworthy figure among the early professors was Jedediah Cobb, a New Englander, who was a great anatomist as well as an artist of ability. He was the first man in this country who gave a systematic course in plastic anatomy.

The plan conceived by the Miami University trustees miscarried most disastrously. To meet the dangers of the unexpected competition, a reorganization of the Medical College of Ohio was effected by the trustees of the latter and, in some manner or other, the newly imported professors of the Miami University Medical School were induced to join the Ohio College. When he saw that the scheme had failed, Drake meekly joined the procession and again became a teacher in the school which he had founded in 1819. At the end of the session he resigned and decided to try another plan to set himself right with the world. The old Cincinnati College listened to Drake's eloquent pleading and opened a medical department in 1835. This school was the climax of Drake's career as a builder of institutions of medical learning. It has been said that this school, which was abandoned in 1839, marked the highest point reached by medical education in the West. The men whom Drake assembled in this great school, were all national celebrities and stars of the first magnitude in their respective lines of work. They were such men as Samuel D. Gross, who in after life as professor of surgery at Jefferson became one of the great surgeons and authors of his time; Willard Parker, who, later on in New York, became a distinguished surgeon; Horatio G. Jameson, one of the founders of Washington Medical College, of Baltimore, Md., one of the most eminent surgeons of his time who will always be remembered as the man who introduced animal ligatures into surgical practice; Joseph Nashe McDowell, Ephraim



McDowell's nephew, founder of the first medical college in St. Louis, matchless orator, brilliant anatomist, famous surgeon of whom Henry Clay once said that he had more brains and less common sense than any doctor in America; and James B. Rogers, afterwards professor of chemistry in the University of Pennsylvania. Men of this caliber were Drake's associates in the Cincinnati College. The school collapsed after four years of glorious existence because it had no facilities for giving bedside instruction. It was barred from the old Commercial Hospital because only the professors of the Medical College of Ohio, which was a state institution, had access to the hospital. The humor of this situation becomes apparent when it is remembered that Drake founded this hospital in 1820.

In spite of difficulties and hardships without end the Medical College of Ohio soon became a formidable rival of the Transylvania school. One of the first graduates of the Ohio College was John L. Richmond, who originally came from New York, but drifted to Cincinnati and became the janitor of the Medical College of Ohio. He worked day and night and finally succeeded in obtaining the degree in medicine. He located in Newtown, Ohio, about ten miles from Cincinnati, and, being a Baptist minister, looked after the physical as well as the religious welfare of the people of Newtown. In 1827 he performed a Caesarean section under the most trying circumstances, saving the life of the mother. *This case is the first authenticated case of its kind in this country.* I had the good fortune of presenting the life and services of Dr. Richmond to the medical profession of Cincinnati, and succeeded in arousing considerable interest. The result was the erection of a monument commemorating Dr. Richmond's famous Caesarean section, in Newtown, O.

In 1827 the first building in the West devoted to medical teaching arose on Sixth street, near Vine, and was the home of the Medical College until 1852, when a larger building took its place. Among the teachers of the Ohio College, even before 1840, were some very eminent men, notably Reuben D. Mussey, the great surgeon; Jared Potter Kirtland, who afterwards went to Cleveland and became one of the great naturalists in the West; and John Locke, the inventor of the electric clock, whose name is known to every American student of the natural sciences; Marmaduke B. Wright, the originator of bi-manual version; Henry Willis Baxley, the founder of the Baltimore College of Dental Surgery, the first dental school in the world, and, last but by no means least, Roberts Bartholow, who saw the light of day in Maryland, became a great medical figure in Ohio and was given back to the East when he had become the leading American therapist of his time.

The history of medical schools in the Ohio Valley is not without its humorous features. The short-lived career of the Evansville, Ind., Medical College (chartered in 1846) was a product of the religious fervor and temperance agitation in those days. Classes were opened with prayer and lessons in anatomy made more interesting by the interjection of an occasional Bible-reading. Students who promised not to use liquor, tobacco and profane language were admitted without

having to pay any tuition. The average medical student found these requirements too exacting. Thus, the school soon closed its doors. After 1823 medical colleges began to multiply in all parts of the country. Joseph Nashe McDowell, brother-in-law of Daniel Drake and nephew of the great ovari-otomist, Ephraim McDowell, started the Missouri Medical College in St. Louis in 1840. In 1841 Charles Pope, a Cincinnati graduate, organized the St. Louis Medical College, which enjoyed a long and prosperous career, and in 1891 became the medical department of Washington University. In 1843 Rush Medical College in Chicago started on its honorable career. In the same year (1843) the Cleveland Medical College, the forerunner of the medical department of the Western Reserve University, was founded. Starling Medical College, Columbus, Ohio, followed four years later. In 1849 the medical department of the University of Michigan, at Ann Arbor, was organized. The Cincinnati College of Medicine and Surgery and the Miami Medical College, both of Cincinnati, were founded in 1851 and 1852, respectively. They have both passed out of existence. The cause of death in the former was marasmus, brought on by medical legislation, which raised the educational requirements for medical students and thus reduced the patronage of medical schools. In the case of the Miami College the final dissolution, euphemistically speaking, was accomplished by a more or less amicable absorption into the University of Cincinnati. It was the humane ending of a long and honorable career.

The question of the share which the West can rightfully claim in the sum total of achievement represented by American medicine cannot easily be answered. The medical West naturally is a derivative of what preceded it. The roots of our accomplishments were in the East. Most of our great physicians and teachers, like Daniel Drake, had the seal of approval set upon them by that undisputed alma mater of American medicine, the University of Pennsylvania. In following the development of medical education on American soil we cannot help but appreciate the tremendously vital part played by Philadelphia in furnishing material, inspiration and life itself to the cause from the earliest times. And in all this wonderful activity of mind and heart there appears the personality of Benjamin Rush, the artist whose beck and call and fine appreciative touch gave life to the picture that was created in those heroic days. As we peer down through the aisles of time, he seems so much greater and more imposing to us than he did to the men of his own time or to those immediately following him. To us he looks every inch a heroic figure of tremendous proportions with a classic, a Hippocratic perfection to every move, to every pose. Even his defects and mistakes appear impressibly sublime. That the work of such a man should have placed the impress of genius on the achievements of a whole century seems but a natural course of development. But what has this to do with the evolution of medicine in the West? Give your thoughtful attention to Philadelphia, to Benjamin Rush and to American medicine and see how complete and mutually supplemental this historical drama becomes, each part generating, containing and perfect-



ing the logic of the other two. History recognizes the towering greatness of Rush and places him at the side of probably a dozen other men who were, like Rush, originators of great movements in medicine. Having gazed upon the earliest events that accompanied the birth and heroic youth of American medicine, turn your eyes to the West and think of Cincinnati, of Daniel Drake, of Western medicine. The stage was larger, the appurtenances fewer and more crude, but what has the ultimate harvest been? In looking back over the early times of Western medicine, the one really great and tremendously persuasive factor is the figure of Daniel Drake. *He* is the subject that makes the whole chapter worth while. From whatever side you see him, in whatever manner you analyze him, as a man, as a teacher, as a writer, as a public character, he is a tremendously impressive and heroic figure. He would have made the same deep impression on a more elaborate stage with a more pretentious environment. He loved the West; he revered the stage-setting of his early childhood; he felt deeply for the people of the West, their ideals of life and patriotism; he was distinctly and characteristically a Western man. But everything he thought, said and did was great and powerful, never imperfect or provincial. As a man he impresses us with the childlike simplicity and sweet accordance of his character. As a medical teacher he stood before the students and doctors of medicine like a Daniel Webster, superlatively convincing in his logic and tremendously constructive even in his denunciations. As a public character he ranks with Henry Clay and will never be forgotten for the part he played in preparing public sentiment for the issue that found its final bloody settlement in the Civil War. As a medical writer he gave us the two-volume treatise on the "Diseases of the Interior Valley of North America." This work still occupies the rank which was accorded to it when it appeared, as being one of the few really original medical books written by Americans. If I were to attempt to tell you how this great work was prepared, my story would be an epic and Daniel Drake would be the hero. Like "Faust," which was the inspiration of Goethe's youth, the ever-present thought of his maturer years and the finished product of his ripe old age, Drake's great work was the realization of a dream which pursued its author throughout his whole professional life. The seed from which it sprang was the little book about Cincinnati which Drake published in 1810. Twelve years later he announced his intention to write his great work and asked the profession of the West to aid him in the gathering of material. Shortly after, he undertook the first of his extensive trips of observation, which he continued year after year for almost a quarter of a century. He covered the whole Western country in these trips, studying the earth, the rivers, the plants, the animals, the air, the sky, the people. There were no authorities to quote from; no reference books to consult. He traversed the land in every direction on horseback, on foot, by boat or railway. He endured hardships and spent time, labor and money in the preparation and accomplishment of his great work. Appreciation is the life-food of genius. Daniel Drake lived long enough to receive it, because the reception of the work by the profession was certainly worthy

of the effort and of the author. In 1850 the American Medical Association met in Cincinnati. Dr. Alfred Stillé, of Philadelphia, chairman of the Committee on Medical Literature, reported on the latest medical publications, and devoted the greatest part of his report to an analysis of Drake's work, referring to it as "an achievement of which every doctor in America should be proud." Drake was present and, upon arising, was greeted with a demonstration such as had never been accorded to any one on a similar occasion. The cheers and the clapping of hands were deafening and lasted for several minutes. Again and again the demonstrations started anew. Finally, when the noise had subsided, Drake wanted to thank his colleagues, but his voice failed him. He seemed to be growing faint and was helped to a chair. He covered his face with his hands and wept like a child. His friends crowded around him. To Dr. Stillé, who wanted to comfort him, he said, when he had gained his self-possession: "I have not lived in vain, but I wish father, mother and Harriet were here." In the hour of his greatest triumph, his mind reverted to his father, his mother and to the wife of his youth, all of whom had died many years before. It was Drake's unconscious apotheosis of himself.

Samuel D. Gross, who knew Drake intimately and has given us a very readable sketch of him, places Drake among the greatest men whom our profession in this country has produced. Gross pens a delightful word-picture of Drake's appearance about the time when he was lecturing at the Medical Department of the Cincinnati College. He was at that time 52 years of age and in full possession of his magnificent physical and mental powers. Gross tells us that Drake was a handsome man, with fine blue eyes and manly features. He had a commanding presence, being nearly six feet tall, having a fine intellectual forehead. His step was light and elastic; his manner was simple and dignified. He was always well-dressed, and around his neck he had a long gold watch chain, which rested loosely upon his vest. He was a great lecturer. His voice was clear and strong, and he had the power of expression which amounted to genuine eloquence. When under full sway, his whole soul would seem to be on fire. He would froth at the mouth, swing to and fro like a tree in a storm, and raise his voice to the highest pitch. With first-course students he was never popular, not because there was anything disagreeable in his manner, but because few of them had been sufficiently educated to seize the import of his utterances.

Gross characterizes Drake by saying he was easy of access, kind and genial, a hater of vulgarity and immorality, a lover of children and of innocent fun, a thoroughly noble Christian gentleman. His modesty bordered on affectation. In 1850 he refused the presidency of the American Medical Association because he did not think that he was worthy of such honor. He did not want to go to Europe because he was afraid of meeting great physicians, men of university education, who had had greater advantages than himself. "I think too much of my country to place myself in so awkward a position." Drake said this at a time when his name was spoken with respect everywhere in England and on the Continent.

Drake was himself in all things. When I say this about him,

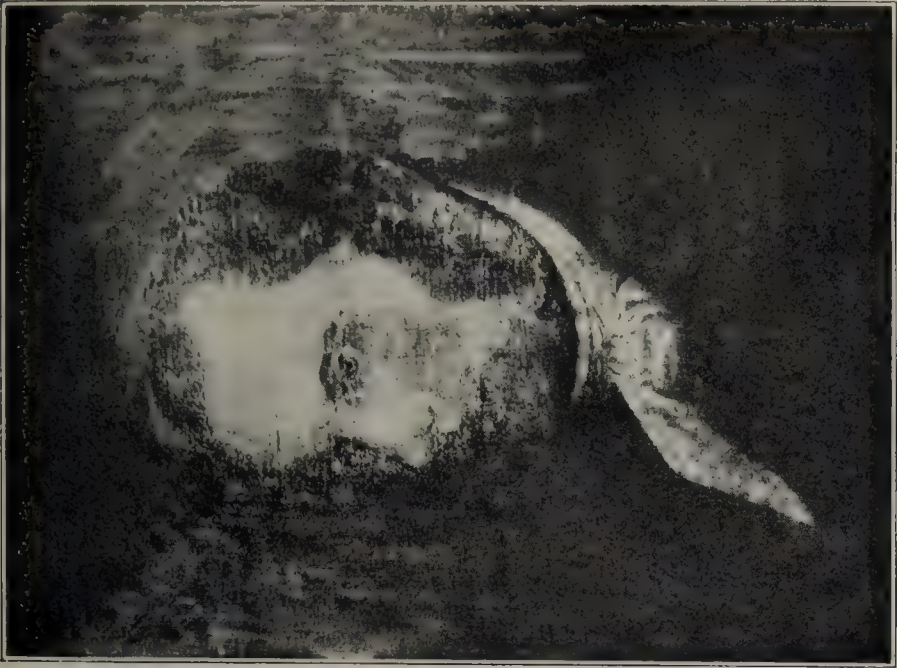




DANIEL DRAKE



HARRIET SISSON DRAKE  
(The wife of Daniel Drake)



JOHN L. RICHMOND  
(The only picture extant. Reproduced from an old oil-painting)



ALEXANDER DUNLAP



THE RICHMOND MONUMENT AT NEWTOWN, O.



BENJAMIN WINSLOW DUDLEY







I must add that the love of Western people and Western ideals was a part of himself. When I have added this, I have given you a complete perspective of the man. When he went to Philadelphia in 1830, to lecture at the University of Pennsylvania, he was not too busy to look for and see things that might be of interest to his beloved Cincinnati. He found John Eberle and brought him, but long before this he had secured a soda-fountain which he brought to Cincinnati as a public attraction and to counteract the inroads of intemperance among the people. He loved Cincinnati and saw in her one of the great cities of the future. He loved her people because they were *her* people. He lived and loved in Cincinnati and the object of his life and his love was Cincinnati. The greatest acknowledgment of Drake's genius, however, should come from the members of his profession. Drake, above all things, was an American physician who spent his professional life in helping to develop all that is true and worth while in American Medicine. No physician from the West had as many friends and admirers in the East as he. Even in Europe his work as a naturalist was widely known and thoroughly appreciated. Towards the end of his life honors and distinctions were literally showered upon him, by the West as well as the East. Drake's labors were ended in the year 1852. In beautiful Spring Grove, Cincinnati's silent city of the dead, he rests beside his own beloved Harriet, beneath a modest shaft of sandstone which to-day is crumbling. Others, whose lives were of no import, have monuments of royal splendor.

And what has been the fruit of Drake's life and labor? The medicine of the West needs no apology. It has added much to our knowledge of practical resources in the treatment of disease. We can boast of a glittering array of Drake's followers who have continued the work of the master and have

left footprints in the sands of time. The father of cholecystotomy, J. S. Bobbs, of Indiana, is one of the many distinguished examples of the medical genius of the West. Nathan Davis, of Chicago, gave us the American Medical Association which has united the disciples of Rush and Drake in the cultivation of the professional, scientific and patriotic ideals of our American profession. Let us not forget Wm. Beaumont, of St. Louis, the father of American physiology. The man who sat at the feet of Albrecht v. Graefe and carried the first ophthalmoscope to London and Paris, afterwards bringing it to this country, thus establishing modern ophthalmology as a distinct specialty, was Elkanah Williams of Cincinnati. Rush and Drake, and with them all the great leaders in American medicine who founded our medical schools East and West; men like Wm. Shippen, John Morgan, Philipp Physick, John Warren, Nathan Smith and John B. Davidge, radiate a specifically American form of public spirit and patriotism that has been of incalculable service, not only to the cause of medicine, but to the welfare of our country. In stepping before you and bringing you the greetings of the West I have tried to let *him* be my spokesman than whom no one understood the West better or loved his native land and all mankind more ardently.

To have been permitted to speak to you about the West and its professional childhood days, is indeed a priceless pleasure. To have had an opportunity of appearing before a distinguished audience of Eastern physicians and of paying homage to our Drake, whose superlative leadership has long been an inspiration to men like Samuel D. Gross, William Osler, James Gregory Mumford, Wm. H. Welch and others of similar caliber, is indeed a privilege which is worthy of a lifetime of endeavor and effort.

## REPORT OF A CASE OF ACNITIS WITH A STUDY OF THE POINT OF ORIGIN OF THE PATHOLOGICAL PROCESS.

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The first description of acnitis was given by T. Fox<sup>1</sup> in 1878, who termed the condition Disseminated Follicular Lupus. He thought it was probably due to the simultaneous predisposition of those affected to acne and tuberculosis, but differed from acne in the following points: (1) its resemblance in color and general aspect to lupus tissue; (2) its indolent non-inflammatory course; (3) its insusceptibility to ordinary acne therapy.

In 1890 Kaposi<sup>2</sup> presented a case of acnitis before the Wiener Dermatologische Gesellschaft, and because of the associated vascularity suggested the name Acne teleangiectodes.

Barthélemy,<sup>3</sup> in 1891, was the first to describe the condition under the name Acnitis, sharply separating it from folliclis. According to him the principal differential points were its

restriction to the face and the deeper location of the pathological process.

Pollitzer,<sup>4</sup> in 1892, believing that the disease had its origin in the sweat glands, coined the name Hydradenitis destruens suppurativa.

Crocker,<sup>5</sup> in 1902, showed a case before the British Dermatological Society of London. He suggested the name Acne agminata, at the same time adding that it was probably the same as Kaposi's Acne teleangiectodes. He also pointed out its resemblance to Fox's disseminated follicular lupus. The condition described by him, however, differed from these in having a more pustular aspect.

Other cases of acnitis have been described as Acne luposa, Lupus miliaris,<sup>12</sup> and Colloid degeneration<sup>6</sup> of the skin.



Pringle's<sup>7</sup> "A Rare Seborrhoid of the Face" and Brooke's<sup>3</sup> cases of "Varus Nodulosus" resemble it in many respects.

As to the pathology, most authors who have studied acnitis carefully agree as to the character of the cellular infiltration, but there is still a wide divergence of opinion as to the point of origin of the pathological process and the etiology is undetermined.

Although we can add nothing new to the latter, our researches have given such definite results as to the location of the beginning lesions that we feel justified in giving a detailed report of the following case.

The patient was a carpenter, aged 47 years. One sister had died of tuberculosis; otherwise the family history was of no importance. In 1908 the patient had had "a touch of pneumonia," and at that time had had an eruption of pimples on the back. After this he had been troubled for a short time with boils. No history could be obtained suggesting a syphilitic infection. His wife, however, had had eleven miscarriages. The children, so far as the parents know, have shown no skin blemishes. A blood test taken from the mother in 1911 was said to be "suspicious of syphilis."

The affection began, in August 1913, with the appearance of a few small nodules at the base of the nose and about the nasolabial folds, and despite treatment with potassium iodide and various salves, the process gradually extended to the forehead, chin and cheeks. There had been no subjective symptoms except a slight tenderness over the nodules when they attained a large size and became secondarily infected.

We first saw him in December, 1913, four months after the beginning of the disease. A general physical examination showed an old fibrosis of the lungs, most likely of tuberculous origin.

Scattered over the face were about 150 nodules which were grouped on the forehead, temples, base of nose, cheeks and chin [*vid.* photograph]. A few were scattered on the sides of the face, eyelids, margins of the ears and on the skin over the mastoid prominences. The scalp was free except for a small number just inside the hair margin of the forehead. The neck, trunk, extremities and mucous surfaces were not affected, and no lesions were found on any other part of the body.

The lesions varied from 1 to 10 mm. in diameter. They were for the most part discrete, although occasionally two or three of the larger nodules were confluent. They were seated on a non-inflammatory base, but in some cases, when the nodules were close together, a slight reddening and thickening of the interlying skin was present.

The lesions consisted of (1) very small nodules, barely palpable, lying at various depths in the cutis. These felt to the touch like fine shot, were freely movable on the underlying structure and the skin over them was not discolored. These early lesions could not be seen at all if viewed by direct light, but when the patient was observed from the side a slight elevation could often be seen over them. (2) Flat, slightly raised papules, varying from 1 to 2 mm. in diameter. These were of a light yellowish-brown color and in some cases were covered with a tightly adherent scale. When pressed upon with a glass slide there became apparent a central whitish opaque area surrounded by a brownish-yellow collar of "apple-jelly" tissue, which was sharply defined from the surrounding normal skin. When the scale was removed, a small opening in the center of the yellowish infiltrate was disclosed and underneath the scale one could frequently see a cheesy-like plug which had occupied the opening. This yellowish infiltrate, consisting of a gelatinous, very friable mass, could be entirely removed with a fine curette, leaving a sharply punched-out opening. This type of lesion was best observed on the forehead. On the chin and sides of the nose the nodules of this size were more elevated and cone-like in

structure and were not usually covered with a scale. Here was seen, under pressure with a glass slide, a small translucent center, resembling a deep vesicle, surrounded by the jelly-like collar. Some of these nodules were pierced by a hair, in which case they resembled the ordinary pustular nodules of acne. (3) Large elevated tubercles, round or oval in shape, varying from .5 to 1 cm. in diameter. These nodules were firm and elastic to the touch or soft and fluctuating. The skin over them, depending upon the depth of the lesion, showed either a slight reddening or was of a dark red color, frequently showing a central pustulation. The softer ones contained a creamy-like, often blood-streaked material and from the firm ones could be removed the above-mentioned brownish-yellow gelatinous tissue, which was similar in every respect to the apple-jelly nodules of lupus tissue.

The blood count showed the normal cell relation. The Calmette reaction was negative, but the skin tuberculin test was positive.

The Wassermann reaction was negative in both the blood and spinal fluid. The cell count, the globulin and the gold-chloride tests for the spinal fluid were negative.

*Histological Examination.*—Seven nodules of various sizes were excised, fixed in formalin, and stained by the usual methods. Of this number three represented the small shot-like nodules, which were just palpable in the skin. These gave the most definite and uncomplicated picture and being the earliest lesions which could be demonstrated clinically, were studied in detail. They averaged about 1 mm. in diameter, lay in the lower half of the cutis and were sharply defined from the surrounding tissue. Their pathological structure was rather sharply separated into three parts (Fig. 2): (1) A central finely granular, homogeneous mass, containing towards its periphery a few picnotic nuclei and nuclear fragments. (2) Surrounding this a ring of cellular tissue, composed of round, oval or large spindle-shaped nuclei of the epithelioid type. These cells often lay in small groups or nests, showing a concentric arrangement. The intercellular substance in these nests had a coarsely granular, amorphous structure, but between them it was more of the connective-tissue type, showing fibrillar formation. In this layer giant cells were occasionally seen. (3) Lying between the above-described ring and the surrounding layer of normal compressed collagenous tissue were variable numbers of small round cells, in which were scattered a few swollen epithelioid cells. The nodule was devoid of blood vessels except in this outside round-cell layer. Occasionally an elastic-fiber fragment was seen in the central necrotic mass. Elastic tissue was absent from the layer of epithelioid tissue.

In the larger nodules the pathological process was not so sharply defined. Here hair follicles and sebaceous glands were involved in the expanding nodules. Groups and strands of epithelioid cells, in which many large giant cells were frequently present, alternated with masses of small round cells. The latter, however, were always thickest at the periphery of the infiltration. In one nodule showing clinically a central pustule, the center was filled with a mass of leucocytes and the picture of an acute inflammatory process was added. Mast cells and plasma cells were only occasionally seen.

One of the small nodules was cut in serial sections and a number of sections from the excised piece of tissue were mounted before the nodule was reached. It was in these





FIG. 1A.—Front View.



FIG. 1B.—Side View.

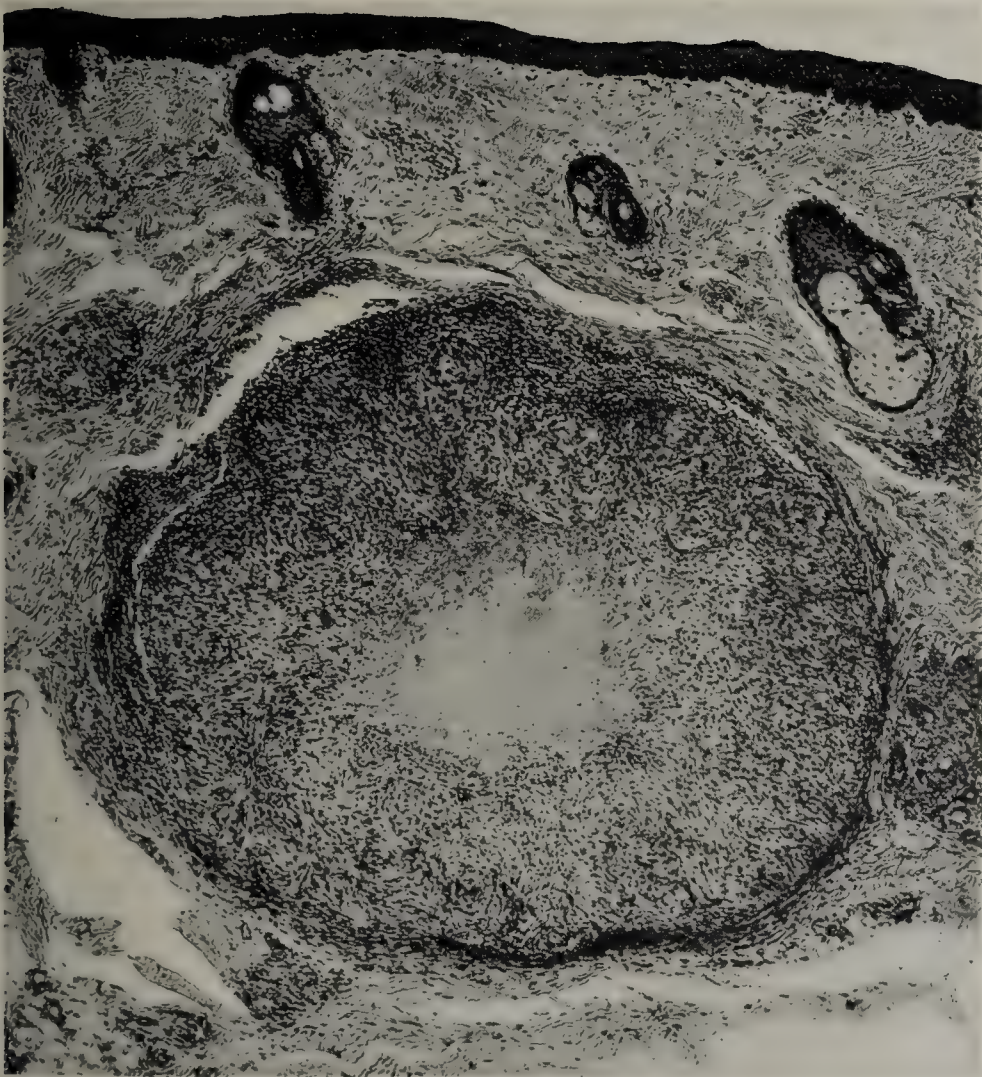


FIG. 2.—Section of one of the small shot-like lesions just palpable beneath the skin.

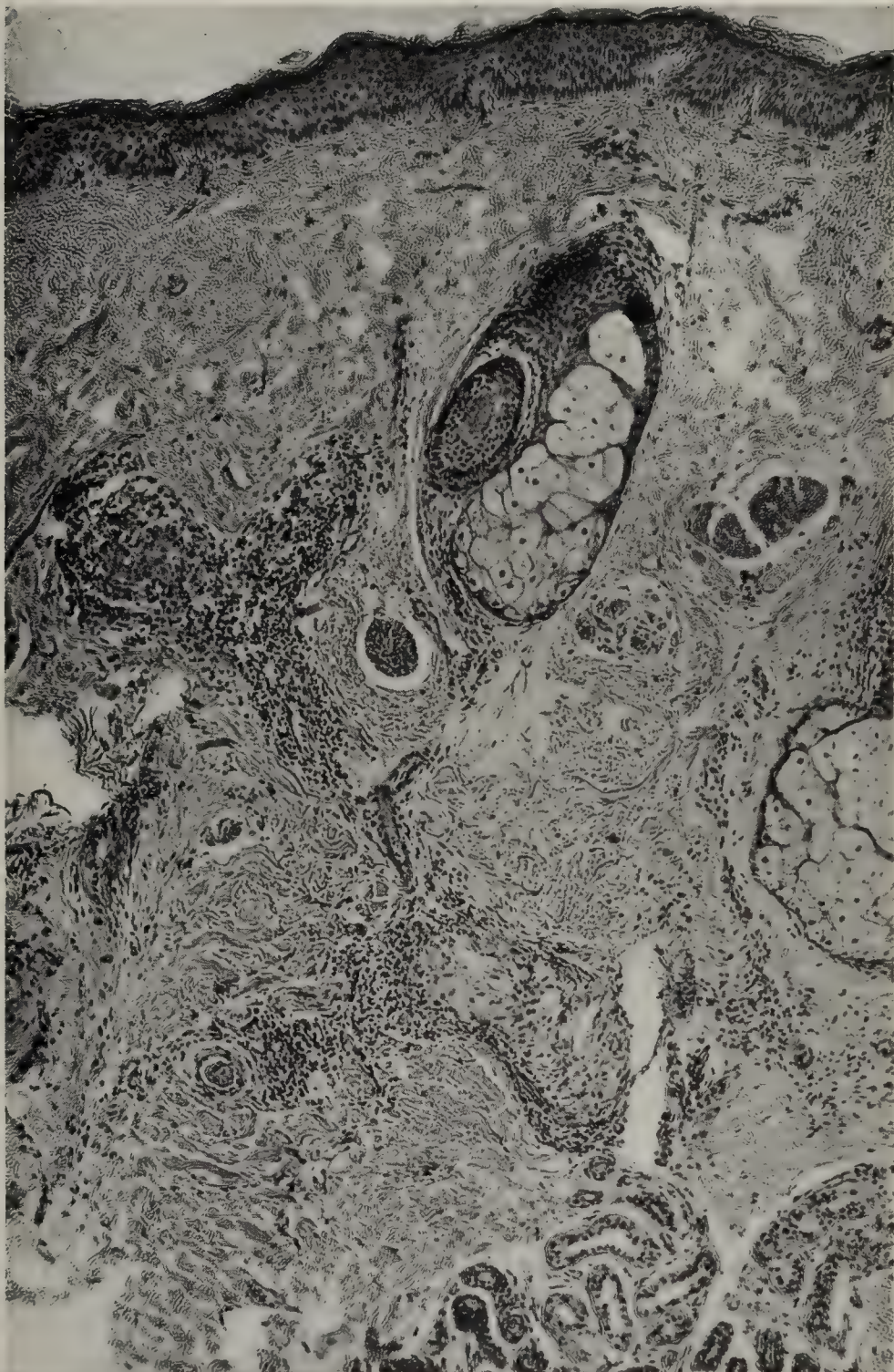


FIG. 3.—Section showing two of the beginning lesions. The upper lesion shows definitely its relation to small blood-vessels.







sections that we were fortunate enough to find three microscopical lesions which gave us the key to the point of origin of the pathological process of acnitis (Fig. 3). One of these lesions lay just beneath the epidermis, another midway in the cutis, and the third in the lower border of the cutis. They were round or oblong in shape and consisted of a small group of epithelioid cells of the same type as those described in the larger nodules. About the periphery were scattered a few small round cells and in one section a giant cell was seen. These small infiltrations could be traced throughout their entire extent in the serial sections and were in no way connected with the sweat glands, hair follicles or sebaceous glands, but lay definitely along the course of the small blood vessels. Two or more vascular branches could be traced into each nodule and in one of them red blood cells were seen lying free in the infiltrate. These branches, before reaching the nodule, became enveloped with a mantle of small round cells, which was continuous with those surrounding the nodule.

As before mentioned, there is a general consensus of opinion as to the chronic inflammatory nature of acnitis, but opinion is very much divided as to the point of origin of the pathological process. This is undoubtedly due to the fact that an insufficient amount of material, especially of the beginning lesions, has been studied. Barthélmey considers the condition a perifollicular process beginning at the base of the follicle. Its deep location differentiates it from folliculitis, which has a more superficial origin. Pollitzer thought that the affection began in the sweat glands and that the giant cells and nests of epithelioid cells were products of the gland epithelium. Pernet, examining one of Crocker's cases, also found the primary changes in the sweat glands. T. Fox believed that "rete, corium and the glands were alike involved in the same morbid process, *i. e.*, the formation of lupoid tissue in their midst." Jesionek<sup>9</sup> found the infiltration around the hair follicles, sweat and sebaceous glands; he suggested that it may have had its origin in the blood vessels surrounding these organs. Spiegler found in Kaposi's case a young granulation tissue surrounding the hair follicles and sweat glands. Finger<sup>10</sup> noted a sharply circumscribed infiltration of giant cells, nests of epithelioid cells and small round cells surrounding sweat glands and hair follicles. In Shamberg's<sup>11</sup> cases the sweat glands were involved, but he was unable to determine whether the process had its origin in these glands or whether they were only secondarily involved.

Our studies show definitely that the primary lesion of acnitis originates in the small blood vessels lying at various depths in the cutis. The varied findings of other investigators can very well be explained by this assumption, as the concerned vessel may surround a hair follicle, sweat or sebaceous gland.

The clinical picture and the pathological microscopical findings show clearly the method of growth and the changes taking place during the development of a nodule. The process begins in the small blood vessels by the formation of a collection of epithelioid cells, which are most likely the result of a proliferation of the endothelium of the vessel and the surrounding connective tissue.

The infiltration extends peripherally, attracting to its outer zone a variable number of small round cells. If it originates in the vessels associated with the hair follicles or sweat or sebaceous glands, the picture is somewhat changed by the enclosure of these organs. Central necrosis soon takes place, owing to the absence of a blood supply in the epithelioid infiltration.

If the lesions lie very superficially and especially where the skin is taut, as on the forehead, a portion of the gelatinous ring of epithelioid tissue soon comes in contact with the overlying epithelium and necrosis is hastened in both from the resulting pressure. Drying ensues, if infection with pyogenic organisms does not take place, and the dead tissue forms the scale and necrotic plug, which is continuous with the central necrotic mass. On the cheeks and chin, where the tissues are looser, the epidermis is less frequently involved until the nodule becomes larger; then secondary infection frequently takes place, as one or more hair follicles are usually involved by the expanding nodule.

If some of the lesions having a deep origin reach a large size without secondary infection taking place, the jelly-like tissue may undergo an autolysis forming a yellowish semi-liquid material resembling pus.

Through the courtesy of Dr. Gilchrist I have studied the sections from a case of acnitis which he investigated in this clinic in 1897. The patient was a woman, aged 42, and the condition had existed for six months. It was limited to the face and the lesions resembled those of the present case, except that no pustules were present. The histological preparations from the small shot-like lesions were identical in structure with those described above. No microscopical beginning lesions could be found, as there was a very narrow margin of normal tissue in the sections.

*Etiology.*—The cause of acnitis is still undetermined. The resemblance of the lesions to lupus tissue has led, in most of the reported cases, to careful search for positive evidence of tuberculosis, but the results have been for the most part negative. One of Finger's patients gave a positive tuberculin test and also developed a tuberculous meningitis during treatment. The author also found, in fifty histological preparations, two bacilli resembling tubercle bacilli.

Besnier<sup>12</sup> obtained a positive inoculation test, but Jesionek doubts his results, as the animal did not die until three months after the inoculation.

Jadassohn's<sup>13</sup> case gave a positive tuberculin test and inoculation of animals was successful. The patient also had a tuberculous proctitis.

Our bacteriological results were entirely unfruitful. Three guinea-pigs were injected intraperitoneally with the excised and curetted contents of the nodules. Two died within two weeks. One was destroyed by the janitor before an autopsy could be performed. The other showed only a few enlarged mesenteric lymph glands. Stained sections of one of these glands showed no evidence of tuberculosis, nor were any tubercle bacilli demonstrable. The third pig was sacrificed after three weeks time; no pathological changes were found.

Examination of a number of stained sections and smears of



the gelatinous contents of the nodules showed no tubercle bacilli; a few cocci were occasionally seen.

Cultures were made from the uninfected nodular contents on the various laboratory media, including Noguchi's spirochæte media, with entirely negative results. Cultures from the pustular lesions gave *Staph. albus*.

The entire gelatinous content of one of the nodules, as well as some of the nodular tissue, ground up in saline solution, was introduced into the skin of the forearm of the patient. Absorption took place completely without any definite inflammatory reaction.

Dr. Gilchrist also examined a large number of sections and smears from his case for the presence of tubercle bacilli, but was unable to demonstrate them; and the results after the inoculation of two guinea-pigs intraperitoneally were negative.

Although our results in obtaining positive bacteriological evidence of tuberculosis in the individual lesions were unfruitful, other evidence, namely, the tuberculous character of the nodules and the fact that the patient gave a positive tuberculin test, as well as showing signs of an old tuberculosis of the lungs, is very suggestive that the disease is a form of tuberculosis. Many investigators, however, Shamberg, Crocker, Barthélemy and others, are not in favor of this assumption.

*Course and Treatment.*—In our patient the condition seemed to have reached its height at the time of his first visit to us. Several small nodules were marked, but no definite increase in size was noticed. The patient was observed four weeks without treatment. He was then given an erythema X-ray dose on one side of the face and sulphur ointment on the other. The side treated with X-ray showed, in two weeks,

a definite decrease in the size of the nodules. The portion of the face previously treated with sulphur ointment was now X-rayed, and after the slight erythema had subsided, he was given the sulphur ointment for the entire face. After an absence of about two months, when he returned to the dispensary, a very decided improvement was noticed. About two-thirds of the lesions had entirely disappeared, leaving, in some cases, especially on the hairy portion of the face, small irregular, rather deep, scars. On the temples and forehead the scars were more shallow, velvety, and slightly pigmented.

At the present time, ten months since the patient was first seen, the disease has in general subsided, but a few small freshly developed lesions are to be seen on the cheeks and eyelids.

In conclusion, I wish to thank Dr. Gilchrist, in whose department these investigations were made, for his personal interest and suggestions.

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## PROCEEDINGS OF SOCIETIES.

### THE JOHNS HOPKINS HOSPITAL MEDICAL SOCIETY.

FEBRUARY 1, 1915.

1. A Simple Method for Determining Variations in the Hydrogen Ion Concentration in the Blood. (Abstract.) Drs. L. G. ROWNTREE, W. McKIM MARRIOTT, and R. L. LEVY.

Serum or whole blood is placed in small collodion sacs and dialyzed for five minutes against a normal saline solution. The hydrogen ion concentration of the dialysate is determined by adding a few drops of phenolsulphonephthalein and comparing the color thus obtained with that produced on adding the indicator to solutions of known hydrogen ion concentrations. A determination by this method can be carried out in a few minutes and requires only from 1 to 3 cc. of blood or serum. The results are, in general, comparable with those obtained by the use of electrometric methods.

The dialysate from normal blood (oxalated) shows a hydrogen ion concentration of from  $10^{-7.6}$  to  $10^{-7.8}$  and the serum dialysate varies from  $10^{-7.6}$  to  $10^{-7.8}$ . In uncompensated acidosis, occurring in the course of diabetes, nephritis, alimentary intoxication in infants and after intravenous administration of acids to animals, the hydrogen ion concentration of the dialysate from serum was found to vary from  $10^{-6.9}$  to  $10^{-7.5}$ . Whole blood under the same conditions gave a dialysate showing variations in the hydrogen ion concentration from  $10^{-6.9}$  to  $10^{-7.4}$ . The intensity of the acid intoxication in these cases as evidenced

clinically was, in general, proportional to the degree of departure of the hydrogen ion concentration from normal values. In all, 25 normal cases, 50 pathological cases without acidosis and 15 cases with acidosis were studied.

2. Practical Results Obtained from the Schick Reaction and the Value of Intraspinal Injections in Tetanus. Dr. W. H. PARK.

FEBRUARY 15, 1915.

### REPORT OF SPECIAL WORK IN THE SURGICAL DISPENSARY.

1. Plastic Surgery and Wound Healing. Dr. JOHN STAIGE DAVIS.

On October 15, 1913, the two small rooms in the Surgical Dispensary, formerly occupied by the Social Service Department, were set aside for those patients requiring special treatment in plastic surgery and wound healing, and also for rectal diseases. Dr. Stone was placed in charge of the rectal work, and the plastic and wound healing work was assigned to me. Each clinic was held three times a week on alternating days. It has been thought advisable to make a short report and the following will show in brief the work done in plastic surgery and wound healing between October 15, 1913, and August 1, 1914:

The *total number* of patients treated was 143; of these 113 were white; 30 were colored. *Sex*: Seventy-five were males; 68 were females. *Civil State*: Fifty-eight were married; 78 were single;



7 were widowed. *Ages:* Under 10 years, 29; 10 to 20 years, 25; 20 to 30 years, 28; 30 to 40 years, 11; 40 to 50 years, 20; 50 to 60 years, 18; 60 to 70 years, 6; over 70 years, 6. Of these 13 were patients referred from the hospital; 5 were admitted to the Johns Hopkins Hospital; 6 were admitted to other hospitals in the city.

*Duration of Lesion.*—From half an hour in the accident cases to 30 years in some of the chronic ulcers.

*Result of Treatment.*—Well, 79; improved, 42; unimproved, 5; not treated, 3; admitted to hospital, etc., 14. The ultimate result of treatment of these patients admitted to the hospitals is not known.

Wassermann reactions were taken on all patients with suspicious ulcers.

#### SUMMARY OF CASES.

*Amputation of Finger, traumatic, partial.*—12 cases: White, 11; colored, 1. Males, 10; females, 2. *Ages:* Between 16 and 50 years. *Occupations:* Operator, 11; laborer, 1. *Location:* Right forefinger, 5; left forefinger, 4; left ring finger, 1; left middle finger, 2; terminal phalanx, 11; second phalanx, 1. *Duration:* One-half hour to five weeks. *Treatment:* Celluloid guard and local measures in 10 cases; well, 10. Plastic operations in 2 cases; both well.

Attempts were made to add to the length of these fingers by training the growth of granulations along a definite line by means of a celluloid tube. Better results were obtained in the instances in which the treatment was commenced shortly after the accident, as the blood-clot molded by the celluloid tube was utilized as a scaffold for the granulations. Gains of .5 to 1.25 cm. were made in the length of the fingers in 10 cases.

*Anchylosis of Wrist, partial, post-operative, infected.*—1 case: Admitted to hospital.

*Angiomata.*—17 cases: White, 17. Males, 4; females, 13. *Ages:* Between 6 weeks to 16 years. *Location:* Forehead, 4; cheek and trunk, 3 each; upper lip, lower lip, scalp, nose, face and finger, 1 each. *Duration:* Congenital, 15; three months and six months, 1 each. *Treatment:* Carbon dioxide ice, 12; well, 4; improved, 8. Excision, 4; well, 3; improved, 1. Not treated, 1.

The comparatively small number of cures in this group is due to the fact that the treatment with carbon dioxide ice requires a considerable period of time, and further applications will be necessary in several of the cases. The treatment is tedious in some instances, but the final result obtained with this agent is most satisfactory.

*Contractures.*—5 cases: White, 4; colored, 1. Males, 3; females, 2. *Ages:* Between 19 months and 59 years. *Location:* Fingers, 2; face, elbow and popliteal space, 1 each. *Duration:* A few months to 10 years. *Treatment:* Plastic operation and whole thickness grafts, 2; well, 1, improved, 1. Plastic operation, 1; improved. Not treated, 2. One of these patients was advised to return for operation, and one, a marantic child, is being built up for operation. There were 3 contractures following burns; 1 had followed operation with infection, and 1 operation for infection.

*Deformities.*—7 cases: White, 6; colored, 1. Males, 5; females, 2. *Ages:* From 2 weeks to 43 years. *Location:* Webbed fingers, 3; of these two were congenital and one had followed a burn. Finger and ear; nose and ear, 1 each, both congenital. Ear, 2; both had followed trauma. *Treatment:* Requiring operation in the hospital, 4. Plastic operation, 3. *Result:* All well.

*Epulis.*—1 case: Lower jaw. Admitted to the hospital.

*Foreign Body.*—1 case: Needle in leg. *Duration:* 6 years. Removed. *Result:* Well.

*Fractures, Compound.*—2 cases: White, 2. Males, 2. *Ages:* 6 and 50 years. *Location:* Left thumb, 1; left middle finger, 1.

The thumb was entirely torn off, except for a narrow strip of the soft parts. *Duration:* One hour and 1 day. *Treatment:* Plastic operation on thumb. Celluloid guard on finger. *Result:* Both well, function good.

*Keloid.*—4 cases: White, 1; colored, 3. Males, 3; females, 1. *Ages:* Two to 38 years. *Location:* Face and chest, 2 each. Two had followed operation, and 2 had followed a burn. *Duration:* Two and a half months to several years. *Treatment:* Carbon dioxide ice, 1; improved. Admitted to the hospital, 1. Advised operation, not treated, 2.

*Mole, extensive, pigmented, of chin.*—1 case. Young baby. To return when the child is older. Not treated.

*Papillomata.*—5 cases: White, 5. Males, 3; females, 2. *Ages:* Eighteen months to 32 years. *Location:* Upper lip, chin, cheek, thumb, foot, 1 each. *Duration:* Four weeks to 10 years. *Treatment:* Carbon dioxide ice, 4. Well, 4; not treated, 1. This patient was sent to the Harriet Lane Home for a general building up.

*Sinus of Neck.*—1 case: The patient stopped coming before complete recovery. Operation advised, but the patient did not return. Result not known.

*Tendon, Destruction of, following infection.*—2 cases: White, 1; colored, 1. Male, 1; female, 1. *Ages:* 40 and 12 years. *Occupation:* Engineer, and schoolgirl. *Location:* Right forefinger, and right middle finger, 1 each. *Duration:* Two months and 5 months. *Treatment:* Plastic operation, 2; improved, 2.

*Ulcer Following Burn.*—13 cases: White, 7; colored, 6. *Ages:* Seven to 80 years. *Location:* Lower extremity, 7; upper extremity, 3; head, 3; trunk, 1. *Duration:* Few days to 6 years. Among these were acid burns, of leg, 2; of cheek, 1. Frost-bite and ice-bag slough, 1 each. *Treatment:* Local, 5; all well. Small deep grafts, 5; 3 well; 2 improved. Local and small deep grafts, 2; 1 well, 1 improved. Whole thickness grafts, 1; well.

*Ulcer Following Infection.*—9 cases: White, 7; colored, 2. Males, 6; females, 3. *Ages:* Nine to 63 years. *Location:* Lower extremity, 9. *Duration:* Few months to 30 years. *Treatment:* Local, 1; improved. Small deep grafts and local, 6; well, 3; improved, 2, unimproved, 1. Two patients did not return for treatment. Two were admitted to another hospital, and one was admitted to The Johns Hopkins Hospital.

*Ulcer Following Operation.*—15 cases: White, 11; colored, 4. *Ages:* Nine to 55 years. *Location:* Lower extremity, 8; upper extremity and trunk, 3 each; head, 1. *Duration:* One week to 3 months. Nine of these were house cases. *Treatment:* Local, 7; 6 well, 1 improved. Small deep grafts, 6; 1 improved, 1 unimproved.

*Ulcer Following Excision of Epithelioma.*—Six patients, all white. Males, 3; females, 3. *Ages:* Fifteen to 82 years. *Location:* Cheek, forehead, 2 each; scalp, finger, 1 each. *Duration:* A few days to two weeks. *Treatment:* One was grafted with Thiersch grafts; 5 were grafted with small deep grafts. All the grafts were successful, and all the patients were discharged well.

*Ulcers, traumatic.*—11 cases: White, 8; colored, 3. Males, 11. *Ages:* From 11 to 72 years. *Location:* Lower extremity, 6; upper extremity, 5. *Duration:* One week to 9 months. *Treatment:* Local, 5; 3 well, 2 improved. Small deep grafts and local, 6; 4 well, 1 improved, 1 unimproved. Three of these patients had been in the hospital. One was admitted to another hospital.

*Ulcers, varicose.*—21 cases: White, 16; colored, 5. Males, 3; females, 18. *Ages:* From 28 to 65 years. *Occupation:* Housewife, 16; laborer, and operator, 2 each; blacksmith, 1. *Location:* All were on the leg. Right leg, 5; left leg, 12; both legs, 4. *Aggravating causes:* Pregnancy, 1; typhoid, 19 years before, 1; milk-leg, 1. *Duration:* Two weeks to 25 years, off and on. Two were admitted to the hospital. *Treatment:* Local, 16; well, 8; improved, 7; unimproved, 1. Small deep grafts and local, 5; well, 4; improved, 1.



*Ulcers of Leg, luetic.*—6 cases: White, 3; colored, 3. Males, 1; females, 5. *Ages:* From 23 to 65 years. *Location:* Left leg, 3; right leg, 3. *Duration:* Few months to 20 years. *Treatment:* Local, 4; improved, 4. Small deep grafts, 2; 1 well; 1 unimproved. Constitutional treatment also was carried out in each case. Several patients were given salvarsan with little beneficial result. Some of the ulcers undoubtedly had originated as luetic ulcers, but had been kept open by poor circulation due to varicose veins, and secondary infection.

*Varicose Veins.*—1 case: Both legs. Male, 54, white. Several years' duration. Advised operation. Refused. Rubber stocking. Improved.

*Warts (multiple).*—1 case: Hands. Treated with carbon dioxide ice. Patient did not return for further treatment. Result unknown.

*Wound, Lacerated, of Finger.*—1 case: *Treatment:* local; well.

#### COMMENTS.

It is obviously impossible in a report of this character to give the treatment of each case in detail, so I will only mention the several methods used.

The following *operative procedures* were carried out: Curettage of ulcers; incision of edges and bases; removal of foreign bodies; excisions; tendon plastic operations; skin grafting, small deep grafts, Thiersch grafts, whole-thickness grafts; plastic operations of various kinds; applications of carbon dioxide ice.

The following *local applications* were used: *Wet Dressings.*—Gauze, wet with 1-500 aqueous solution of iodine; boric acid solution, 2 per cent; 1 per cent dahlia (basic fuchsin and methyl violet); 1 per cent basic fuchsin; 1 per cent methylene blue; 1 per cent gentian violet (methyl violet and dextrin); 48 per cent glucose solution; glycerine; olive oil; neutral paraffine oil.

*Ointments.*—Boric acid ointment; zinc oxide ointment; ammoniated mercury ointment; blue ointment; scarlet red, 4 and 8 per cent; amidoazotoluol, 2 per cent; azodolen, 2 per cent; pellidol, 2 per cent; dimazon, 2 per cent; balsam of Peru.

*Stimulants and Disinfectants.*—Tincture of iodine; nitrate of silver; pure carbolic acid.

*Miscellaneous.*—Old linen; rubber protective; paraffined mesh; paraffined linen; sheet celluloid.

*Retentive Dressings.*—Gauze and muslin bandages; stockinette; adhesive plaster.

The hot air douche was used with considerable benefit in some cases.

The treatment was often handicapped by the fact that the greater number of these patients were compelled to continue their daily occupations, and thus the most important factor, rest, was eliminated. Many of the patients have been regular in attendance and have cooperated in every possible way, but others have been most irregular in attendance, and several have not returned after the first dressing. There was no way of following up such cases, but I am glad to say that recently a social service worker has been assigned to the surgical out-patient department, who will be of great assistance in this respect.

A considerable number of these patients needed hospital treatment, especially those with chronic ulcers. There are but few beds available for such patients in this hospital, or in any other hospital. The maintenance of a ward for the scientific treatment of these cases would be a charity which would be far-reaching in its beneficial results.

New and intensive methods of treatment have been tried. The willingness of the patients to allow operative procedures in conditions heretofore treated locally, speaks for the success of the results they have seen on others.

Many of the ulcers treated were of long duration, and offered

a most unfavorable field. Some of the patients had been coming to the dispensary for as long as fifteen years.

Some of these lesions have been cured, and others have been much improved. Fingers and hands have been made useful. Disfiguring angiomas have been removed.

Taking into consideration the number of years many of these patients have been coming to the dispensary for treatment, and their successful treatment in a comparatively short time by special methods, we have reason to feel encouraged. Furthermore, the economic saving to the hospital, both in time and material, to say nothing of the great benefit to the patients themselves, from the wage-earning standpoint, would seem to justify the work.

Both Dr. Stone and myself wish to thank Dr. Seem for his help in making this work possible, and the staff in the Surgical Dispensary for their cooperation.

#### 2. Rectal Surgery in the Dispensary. DR. H. B. STONE.

In October, 1913, concurrently with the start of the work that Dr. Davis has just described, it was decided to segregate the rectal cases in the dispensary from the rest of the general surgical material. Since then Dr. Davis and myself have used the same rooms on alternating days and the two subjects have been handled in a more or less parallel manner. The new arrangements have provided more adequate conditions for the examination and treatment of rectal diseases than existed before, and it is the purpose of this paper to present the experience of the ten months of last year during which the present plan has been in operation, with a few brief comments. The material comprises a little over one hundred cases. It will be noted that very few rare conditions are included in this list and that even cancer of the rectum is not represented by a single instance. The fact that there is so much rectal work at present in a dispensary, which until now has made no attempt to encourage especially the development of this field of surgery, is rather surprising and there is every reason to believe that the volume of material from this time on should show a steady growth. One might question how feasible the treatment of these conditions in an out-patient department would be; and the purpose of this paper is to discuss this point, as well as to illustrate the economic saving to the hospital involved in the treatment as dispensary cases of many patients, who formerly were sent into the house and occupied beds for periods ranging from one to two weeks.

To make clear these points it is perhaps best to consider the individual groups of cases in order.

*Abscess.*—18 cases. Of these patients, only two, in whom the abscesses extended far up the bowel wall and were of considerable size, were sent into the hospital. The rest were handled without difficulty as ambulatory patients, the original operation being performed, usually with ether anesthesia, in the dispensary and the subsequent dressing being done at regular intervals thereafter. These patients complained of no great difficulty in going to and from the dispensary and in no case was there any reason to feel that the welfare of the patient was at all jeopardized by his coming back and forth.

*Condylomata.*—3 cases. In one case the growths were specific (condylomata lata); in the other two they were benign papillomata of the acuminate type. All of these patients were treated under ether. In the first instance the specific lesions were destroyed by means of the actual cautery. In the other two cases the tumors were excised and the bases cauterized to control hemorrhage and also to restrain any tendency to local recurrence.

*Dysentery.*—The one case met with was of the amebic type. The patient was sent into the hospital for treatment.

*Eczema.*—The one case was treated with local applications.

*Fissure.*—8 cases; all were very satisfactorily treated under local anesthesia. This work was first done with novocain.



Recently we have been using a mixture of novocain and quinine urea hydrochloride (1% of each). This gives a very satisfactory anesthesia which not only permits perfect freedom in the local field to be operated on, but also allows good dilatation of the sphincter. There was no class of patients more grateful than these for the relief secured by this very simple and safe surgical procedure.

*Fistula.*—20 cases. Several of these were of the multiple type; one or two were definitely associated with pulmonary tuberculosis. The patients showing such extensive processes were sent into the hospital, the others, who constituted a majority of all the patients seen, were operated on in the dispensary, many of them with local anesthesia. Even in those cases in which the sphincter was divided, this form of anesthesia was amply sufficient. There were no unpleasant consequences observed from sending patients home after such operations. The method of handling these cases after operation will be considered in detail later. No cases of incontinence resulted in this series of operations. In this connection I wish to express my belief that fistula is best treated by an incision radiating from the anus instead of tangential to it.

*Foreign Body.*—2 cases. In one case the foreign body was a fish bone; in the other a small fragment of meat bone. There was nothing of particular interest in these cases except the mechanical difficulty in dislodging the bones, which were buried in the tissues.

*Hemorrhoids.*—31 cases. These fall naturally into two clinical divisions, the external and internal types. All of the external type were operated upon in the dispensary under local anesthesia without difficulty and with satisfaction to the patient. In reality these cases present no greater problem than arises in the case of a small benign tumor elsewhere on the body surface. It is to be noticed that thrombotic piles should be excised, rather than incised and the clot removed. In the latter case the cavity left by the thrombus not infrequently becomes filled with clot again, giving further trouble. As to the internal cases, we have divided them into three groups according to the method of treatment best suited to the case. First, there are the very mild cases which bleed only at rare intervals and occasion very little subjective discomfort. These cases, when examined, present only moderate anatomical changes and for them a non-operative method of treatment is desirable. This consists in the use of some local application, containing sedative and astringent drugs, combined with the use of cascara or some other form of mild laxative to diminish the traumatism of defecation. Under such treatment the patient, although not cured, is certainly rendered free from any symptoms for a long period of time. The second group is made up of cases in which there are one or a few masses of localized tissue, easily accessible and definitely circumscribed. Such cases we have treated in the dispensary by removing the tumor masses under local anesthesia and securing the blood-vessels by means of catgut sutures. These patients have been allowed to go home, and in no instance so far has there been any subsequent trouble. The possibility of hemorrhage has always been borne in mind, but care is taken to secure good hemostasis at operation and growing experience is making the probability of such a complication as secondary bleeding seem remote. The last group of internal piles are those in which there is a large and extensive development of varicosities or perhaps a complete circle. These patients we have not felt justified in operating on in the dispensary, and up to the present time they have been sent into the hospital. Nevertheless, I believe that it would be entirely practical to carry out the operative treatment of these cases, as well as of numerous others, were we provided with a small 24-hour ward, where two or three beds with the necessary adjuncts could be utilized for retaining over night patients operated upon in the dispensary.

*Papillæ.*—This condition of hypertrophied anal papillæ, which is emphasized in many text-books as a cause of numerous rectal

symptoms, has been encountered only three times, at least when it was of sufficient development for us to recognize it as a probable cause of trouble. It is dealt with under local anesthesia.

*Pilonidal Sinus.*—The one patient who came to us during the past year suffering from this condition, was sent into the hospital for treatment.

*Poison Oak.*—One case was treated with local applications.

*Polyp.*—There were two cases of this type, one of which was exceedingly interesting. The patient had had a growth from early childhood, which projected out of the anus for several centimeters, and had its attachment above the internal sphincter. Both of these cases afforded very satisfactory results with local anesthesia.

*Proctitis.*—There were two cases, both of the ulcerated type, diagnosed through the protoscope and sent into the hospital for treatment.

*Prolapse.*—Four cases; the patients were all sent to the hospital for treatment.

*Stricture.*—Two cases. In one of these the stricture was due to a thin but very firm scar following a Whitehead operation. This was divided, under ether, and forcibly dilated in the dispensary. The other case was of specific origin and presented a tubular stricture with a very small lumen about 1 cm. long. It was satisfactorily treated by repeated gradual dilatation with hard rubber dilators, in addition to the general treatment of the disease.

*Ulcer (anal).*—One case, probably tuberculous, was seen. This ulcer was excised under ether and the base cauterized.

*Wounds.*—There was one such patient treated, the injury resulting from a fall and the condition presenting no especial point of interest.

In all the cases in which operative procedures were employed, the wounded surface was packed with iodoform gauze; over this ample dressings were applied and the buttocks bound firmly together with adhesive. The patients were told to return on the third day and in the meantime were given a lead and opium pill three times a day. Upon their return the dressings were removed, the pack was displaced, the wound washed and new dressings were applied, but this time a T-bandage instead of adhesive was employed. The patient was then given cascara with directions as to the management of his dressings at home. This early start in the use of laxatives has not been followed by any disadvantage, but on the contrary seems very much better than the older custom of longer delay. In fact the absence of any severe pain when the bowels began to move has been a very noticeable feature of the post-operative history in nearly all cases.

This somewhat superficial report of the first ten months' work in this department brings forward several points that are worthy of emphasis. In the first place the provision of a room and equipment, adapted for the performance of rectal work, has considerably extended the range of material that can be treated in the dispensary and hence has increased the teaching facilities for third-year students. This teaching can be done in a much more direct and personal manner than is possible when these cases are handled in the general operating room. Further than this, the hospital is relieved of a considerable number of bed patients, who may now be satisfactorily cared for in the out-patient department. This economy and the advantage of such a change need not be dwelt on. Lastly, the possibility of improvement in managing the surgical problems, presented in this especial field, should be enhanced by the opportunity of seeing a larger amount of clinical material and possessing better facilities for handling it.

#### DISCUSSION.

DR. EARLE: I congratulate The Johns Hopkins Hospital in having organized in their dispensary this special branch of rectal work. A few years' experience will teach any of you, after you have taken up



general practice, just how much need there is for such instruction as you receive under Dr. Stone in the dispensary. We see over and over again in our practice the grossest ignorance of otherwise well equipped and well qualified physicians, and even surgeons, in the treatment of rectal diseases. As Dr. Stone has shown you, these cases can be treated, and are being treated at the office by those who are following this special line of work. Many patients have heretofore been confined to bed from two to three weeks for operations that could readily have been performed under local anesthesia in the office. I can only hope that you, as students, will avail yourselves of the opportunity Dr. Stone offers you for learning to deal with these cases intelligently and to discern between the gross and the minor lesions, so you will be able to treat these patients properly in your office and with as little delay from their business as is possible.

There are some things that must be especially borne in mind in rectal surgery; among them, the fact that you are always working in a field that it is almost impossible to make sterile. In these cases you have to supplement the means used in the treatment of wounds in other portions of the body with much closer supervision, remembering that one cannot close up a wound here and expect to uncover it in five or six days, with primary union, but that frequent antiseptic washes must be used and, above all things, that the bowels must not be confined too long, as was formerly the custom. It must be borne in mind that these cases should receive personal and frequent attention, and it is chiefly by such means that those who follow this line of work obtain good results.

I congratulate Dr. Stone upon his work and hope it will continue. There is great need for just such effort as his, and I am glad to see it recognized by this hospital.

### 3. \* A Study of the Ferments and Anti-Ferments of the Body and Their Relation to Certain Diseases. DR. J. W. JOBLING.

## THE JOHNS HOPKINS HOSPITAL HISTORICAL CLUB.

FEBRUARY 8, 1915.

### 1. The Times of Vesalius. Contributions of Vesalius Other than Anatomical. DR. WM. H. WELCH.

It seemed a pity not to devote one of the meetings of our historical club to the celebration of the four hundredth anniversary of the birth of Vesalius. It was intended to commemorate this on a fitting scale in Belgium during the month of December when preparations had been made and interesting exercises had been arranged for in Brussels and at the University of Louvain. It is sad beyond measure to contemplate the situation which rendered it impossible to carry out that intention. However, in this country we have endeavored to do our best in the celebration of this event, exercises having been held in Boston, New York, Washington, and I believe elsewhere.

In these introductory remarks, it seems appropriate to say a few words about the times in which Vesalius lived and did his work, also of his contributions other than those to anatomy.

As you know, Vesalius was born on the last day of December, 1514, and died in 1564. This was an extremely interesting and stirring period. It was the early part of the period of the French Renaissance, the zenith of the Italian period having been reached in the preceding century, or not later than the year 1500. There were a number of events that, taken together, combined to make this one of the most stirring periods of all human history. About the middle of the fifteenth century printing had been invented, and coincident with that was the invention of cheap paper, so that the rapid spread of books, writings and knowledge was made possible. Toward the end of this century—indeed

throughout its latter half and the early part of the sixteenth—came the discoveries of the great Spanish and Portuguese explorers, opening up a new world. About the middle of the sixteenth century, 1543, the very year of the publication of Vesalius' great work, the epoch-making contribution of Copernicus established the Copernican system, that theory of the solar system which was eventually to take the place of the Ptolemaic theory. Another great influence to open men's minds to new knowledge was the revival of classic learning—one of the most striking characteristics of the Renaissance. The writings of Hippocrates, of Galen and of Aristotle were made known as they actually existed and were not deformed by passing through many translations. It was not uncommon to have these writings translated from Greek into Syriac, from Syriac into Arabic, thence into Hebrew and finally into Latin before being made known to the medieval mind. It is easy to see how distorted the point of view must have been. This revival of classical knowledge brought into prominence one book of great significance for that period which had previously been very little known—the great work of Celsus on medicine.

This was also the period of great painters and sculptors, the age of Raphael, of Titian, of Michael Angelo and of Leonardo da Vinci, indeed one of the greatest periods in the world's history of art. It is interesting to note that this artistic development had great influence upon anatomy. The artists themselves were often anatomists and loved to make anatomical drawings. Leonardo da Vinci, the most varied genius probably who ever lived, a miraculous combination of art and science, apparently manifesting every capacity of the human mind, ranks as a great anatomist. The importance of his work in anatomy was hardly appreciated until his plates were studied by William Hunter in the eighteenth century. The development of art undoubtedly had a most stimulating effect on anatomical drawings and illustrations and in that way on the development of anatomy. It was surmised at one time that some of the plates in Vesalius' *Fabrica* had been made by Titian, but I believe this has been disproved.

This was also a marvelous period in literature, both in poetry and in prose. It is interesting to recall that one of the great names of French literature, Rabelais, was a medical man and a contemporary of Vesalius. Rabelais partly edited an edition of Hippocrates and himself dissected. He was a teacher in Montpellier, where he had also studied, and was actively identified with the profession of medicine.

As regards science, this was not the great period for natural and physical science, but rather a period of reawakening—a transitional period. The roots of the great developments of the following century are to be sought for in the sixteenth century, but the sciences of observation and the descriptive sciences like anatomy, botany, zoology, and to some extent geology and mineralogy, all had notable development at this time. Leonardo da Vinci was one of the greatest figures in the development of geology.

In botany it was the fascinating time known as the age of the herbalists, a collection of whose works forms a most interesting task for the book lover. The herbalists had great influence on anatomy. Indeed most of them were physicians.

Modern zoology dates from Gessner and Aldrovandi. Gessner was a contemporary of Vesalius and was a great botanist as well as a great zoologist. His botanical works were not published until much later, but his zoological works appeared during the sixteenth century.

With regard to medicine, this was also an interesting age. We think of the humanists in medical history as a particularly characteristic and charming type. They were good physicians and among them there is no better example than our English hero, Thomas Linacre, who founded the Royal College of Physicians in the reign of Henry VIII. The medical humanists were characterized by love of classical learning, and often believed that the

\* To be published later in the BULLETIN.



salvation of medicine rested on going back to the writings of Hippocrates, of Galen and of Celsus.

This was a time also when certain diseases either became known or else were accurately studied for the first time, and we find something approaching a good portrayal of disease based on accurate observation. That, of course, was not the dominant note, but this characteristic may be picked out in the writings of certain physicians. A good example is the monograph of John Caius, the founder of Caius College, on the sweating sickness. About the end of the fifteenth century syphilis began to spread with appalling severity, and the study of this disease was taken up by a number of physicians. It was found to be quite irreconcilable in its interpretation, and especially in treatment, with the prevailing Galenic doctrines of pathology. The study of these epidemics, then, marked a certain attack upon the authority of Galen.

The three great names of the sixteenth century in medicine are those of Vesalius, Paracelsus and Ambroise Paré, all others being more or less overshadowed by them. There are other interesting names also, as we pathological anatomists like to recall. That of Frascatorius, for instance, who is one of the most fascinating of figures. I do not believe justice has been done to him yet. He lived in the humanist circle in Florence and also in Padua. He was a poet and wrote on a subject that would hardly be conceived as admitting of real excellence—syphilis—but the work is conceded to have actual poetical merit, besides being historically important from the fact that we date the name syphilis from this poem.

As I said before, Paracelsus was one of the greatest figures of this period—that iconoclastic genius, typical perhaps of the German Reformation, who is sometimes spoken of as the Luther of medicine, and who was the enemy of Galen, Aristotle, in fact of all authority. The Germans give him, I think, a degree of influence which others are not inclined to allow, and he was indeed a remarkable character.

Ambroise Paré is another of the great figures. He is identified with the history of surgery. The life of Paré is a fascinating study in many ways. It is interesting to remember that his is one of the well known names in French literature. In books of French prose of the sixteenth century, you will find that Paré figures as one of the writers of terse, vigorous prose at a time when French prose was being established as an adequate medium of expression.

However, our main interest lies with Vesalius. He was born in the city of Brussels, and was of German ancestry. His father was Court Apothecary to Charles V, and it is evident that the family had some influence. Vesalius received his education in classical studies at the University of Louvain. This was the usual education of the day—Latin, Greek and mathematics. That which has come to be known as our modern system of liberal studies was practically worked out at this period of the Renaissance. Louvain was not noted as a university for humanistic studies. Indeed Erasmus, who was there at this time, felt much more at home in Holland, or in Bâle.

In about his eighteenth year, Vesalius went to Paris for his medical education. Here he was the pupil of Jacobus Sylvius. Other teachers at that time were Jean Guinter Andernac and Fernel. At Paris, Vesalius was a fellow pupil of Servetus, the discoverer of the lesser circulation from the right to the left heart. Vesalius pictures this period of his studies at Paris as lamentably deficient. He describes his teacher, Jacobus Sylvius, in a most unattractive light and says that his opportunities for study were poor indeed. The picture that Vesalius gave of Sylvius is the traditional one, although I believe there is some reason to think that it may have been overdrawn. When Vesalius had been in Paris for about three years, the war between Francis I and Charles V broke out, in consequence of which Vesalius returned to Louvain, where

he remained for about a year. He also served for a few months in the army of Charles V.

About 1537 Vesalius reached Venice and the next six years form the most productive period of his life. The university belonging to the Republic of Venice was at Padua, where the spirit was probably freer than that in any other part of Italy. After having been appointed to make public dissections at the University of Padua, Vesalius was made professor of surgery, including anatomy. John Caius was a pupil of Vesalius at this time. Another interesting contemporary, although a little later, was Montanus, who taught medicine by bedside instruction. The history of clinical teaching dates from this period at Padua. It was during these years that Vesalius prepared his great work, the *Fabrica*, which was published in 1543. Before this he had published another work, the *Paraphrases of the Ninth Book of Rhazes*, which was practically an inaugural dissertation. Vesalius received the degree of M. D. in Padua, although he had previously received it in Bâle. This first publication of Vesalius was a type of work very common in those days, being partly a translation and partly a commentary. For his work he selected the most interesting book of Rhazes, that relating to the treatment of disease. This appeared in 1537. It was in 1539, I think, that Vesalius published a little work entitled *An Epistle on the Selection of the Vein to be Bled*. It is interesting from the fact that he took part in a discussion of that century between the Arabists and the Galenists, or the anti-Arabists. The doctrine of the Arabists was that known as revulsion, which claimed that in bleeding, especially in pleurisy (probably what we would now call pneumonia) the patient should not be bled on the side where the pain was felt, whereas Hippocrates had taught that one should bleed on the side of the disease, or on the side of the pain. This may seem but a trifling matter, but it shook the entire continent. Popes were appealed to, Charles V was asked to give his judgment—indeed it is one of the most interesting examples of the state of mind of medical men of the period in their attitude toward the writings of the Arabist physicians and in their going back to Hippocrates. Vesalius was against revulsion.

The dedication of the *Fabrica* to Charles V was written in 1542 and Vesalius went to Bâle to superintend the publication by the firm of Herpst, one of the publishers of the day. The printers in those days were wonderful men and scholars of the highest rank. Among them were the Aldines in Venice, one of them a great anatomist also. It is known that Erasmus went to live in Bâle because of the publishing firms there. Vesalius' *Epitome*, nowadays an extremely rare volume, appeared in 1543.

From the time that Vesalius secured his leave of absence to go to Bâle, a most extraordinary change took place in his life. He was at that time in his twenty-ninth or thirtieth year, which marked the end of his career as a productive worker. When he went back to Padua his work had been published. It produced a great sensation, because the essential characteristic of his attitude is his correction of the errors of Galen, based upon actual observation of human dissections. Vesalius really made modern anatomy. It has gone on developing continuously from that period. Indeed he gave it a prominence in the medical curriculum which it is only just beginning to lose. For years it was the only subject the students came into contact with directly by observation, and so it had an educational value that no other subject could have.

The publication of the *Fabrica*, as I said, raised a storm. Vesalius' own teacher, Jacobus Sylvius, published a scandalous attack upon him. That is where Sylvius did himself great harm. One of Vesalius' pupils, Columbo, was a great antagonist and apparently an intriguer. When Vesalius returned to Padua, he found the situation exceedingly unpleasant and became greatly discouraged; it is not apparent why he could not have gone on lecturing, but



he was greatly disheartened and burned his manuscripts. His career practically ended here, although he lived until 1564. He afterwards became Court Physician to Charles V and had a lucrative and probably fashionable practice, but his life as a man of science was over, all of his work having been done before he was 30 years of age. A most excellent description of Vesalius is to be found in a volume by Sir Michael Foster, *Lectures on the History of Physiology*. It is supposed that a very attractive offer from the emperor may have had something to do with Vesalius' withdrawal from his chair at Padua. After this, his most interesting publication was the one on the China root, with which he treated the emperor. The book contains a great deal of personal matter for the biographer of Vesalius and makes interesting reading of the times.

In 1563 Vesalius started on a pilgrimage to Jerusalem, no one knows exactly why. The most common theory is that in making a post-mortem examination and opening the chest, the heart was found beating. In other words he was doing a vivisection, supposing he was making a post-mortem. It is said he was brought before the Inquisition and that, the emperor having used his influence, he was told if he would go on a pilgrimage the proceedings would be stopped. Another explanation is that his domestic life was exceedingly unhappy and he seized an opportunity to escape. Still another version has it that his court life had become wearisome to him. At any rate he started out on this so-called expiatory pilgrimage. He went to Venice first and there received an offer to come back to his old chair at Padua, which he agreed to do on the completion of his voyage. On his way to Jerusalem he was shipwrecked, however, and died on the Island of Zante.

Sir Michael Foster in the first chapter of his *Lectures on the History of Physiology during the Sixteenth, Seventeenth and Eighteenth Centuries*, speaks of Vesalius more than once as the founder of physiology, by which he means the founder in the sense that a knowledge of structure is essential for the development of physiology. It is not meant in the sense that he made important contributions to our knowledge of the activities and functions of organs. Of course with that conception, Vesalius' work was epoch-making for physiology, just as it was for medicine in general. Vesalius was essentially Galenic in his physiology. This is what he says of the central point in the Galenic doctrine of the physiology of the circulation. In that doctrine the blood is made to pass from the right ventricle to the left ventricle through invisible pores in the septum between the ventricles. Vesalius says:

"The septum of the ventricles, composed as I have said of the thickest substance of the heart, abounds on both sides with little pits impressed in it. Of these pits, none, so far at least as can be perceived by the senses, penetrate through from the right into the left ventricle, so that we are driven to wonder at the handiwork of the Almighty, by means of which the blood sweats from the right into the left ventricle through passages which escape human vision."

This is interpreted usually as unintentional sarcasm, but Vesalius has nothing to substitute for the view of Galen. However, he tells us in a later writing that "he accommodated his statements to the dogmas of Galen," not because he thought that "these were in all cases consonant with truth but because in such a new great work he hesitated to lay down his opinions and did not dare to swerve a nail's breadth from the doctrines of the Prince of Medicine."

We owe to Foster the credit for calling attention to certain contributions of Vesalius to physiology. He writes as follows:

"That physiological problems were before his mind, that he had thought over, and indeed had tried to solve them by experimental methods is shewn in the brief chapter 'Some Remarks on the Vivisection of Animals,' which is the last chapter in his great work. In this he relates his experiments on muscle and nerve,

showing that that which passes along a nerve in order to bring about movement passes by the substance and not by the sheath of the nerves. He tells us that it is through the spinal cord that the brain acts on the trunk and limbs, that an animal can live after its spleen has been removed, that the lungs shrink when the chest is punctured, that the voice is lost when the recurrent laryngeal nerve is cut, that by artificial respiration an animal can be kept alive though its chest is laid wholly bare, and that under these circumstances a heart which has almost stopped beating may be revived by the timely use of the bellows.

"Obviously his vigorous and active young mind was starting many inquiries of a purely physiological kind, and he was aware that much of the physiology which he had put into his book would not stand the test of future research. He knew more particularly that the chapter in that book in which he treated of the use of the heart and its parts was as he says 'full of paradoxes.' But he was no less aware that his bold attempt to expound the plain visible facts of anatomy was of itself enough to raise a storm of opposition; he feared to jeopardize his success in that great effort by taking upon himself further burdens."

You will observe that Sir Michael Foster attributes to Vesalius' Galenic explanations in describing the structures to the fact that he did not wish to jeopardize the success of his great work by any deviation from more or less canonical authority. Foster also comments on the fact that Vesalius was ahead of Descartes in the idea that the mental activities were a product of the brain.

Another very interesting side of Vesalius is that he was an anthropologist. He was much interested in the shape and character of the skull and noted in his examinations the flattening of the occiput which he regarded as characteristic of the German race. The type of Germans he examined, however, probably belonged to the Alpine race.

## 2. The Relation of Vesalius to Anatomy and Anatomical Illustration. (Illustrated.) DR. FRANK BAKER.

Andrew Wesel, better known to us by his Latinized name Andreas Vesalius, was born in Brussels on New Year's morning 400 years ago. The main facts of his career are well known: how after a preliminary course at Louvain he studied anatomy in Paris under Jacobus Sylvius and Günther von Andernach, returned to Louvain, and afterward went to Padua where he was appointed professor of surgery when only 22 years old, and conducted public anatomical demonstrations both there and at Bologna, and at 28 years of age, published that stupendous, monumental work, the *Humani Corporis Fabrica*.

When a mere boy he dissected mice, moles, rats, cats, and dogs, and it was probably by this means that he acquired that skill of manipulation that enabled him to demonstrate so rapidly in public where, contrary to the usual practice of the time, he always performed the work himself.

The *Fabrica* is a work remarkable not only for its text but also for its illustrations which are totally different from anything previously seen, as they delineate the structures accurately and naturally. Previous illustrators contented themselves with diagrammatic figures of an almost childish character showing details often supposititious, while in the *Fabrica* we have a pronounced artistic method and a treatment so forcible, robust and true that the work has been ascribed to Titian and other great artists of the period. The illustrations are now generally thought to have been done by Jan Stephan van Calcar, a Flemish pupil of Titian, but there are strong reasons for supposing that they were largely the work of Vesalius himself. It is known that he could draw, as his first publication, a commentary on a pharmacological book, was illustrated by drawings of plants; in his public lectures he used large drawings to show relations of organs not yet exposed, and he was accustomed to mark on the cadaver the outlines of the



bones and the joints. Throughout the *Fabrica* he nowhere mentions van Calcar, and moreover the illustrations could only be made by a person perfectly familiar with the anatomy of the parts shown. Skill in drawing is not infrequent among anatomists. Just prior to the time of Vesalius the great artists of Italy, Leonardo da Vinci, Michael Angelo, Raphael and others dissected the human body to perfect their knowledge of exterior form and of action. Leonardo's drawings of his dissections are so accurate that it has been alleged that Vesalius plagiarized from them. Such a charge is evidently untenable, as those drawings were carefully concealed and have only recently been published. Their very legends are so written as to be intelligible only to the initiate.

In the text of the *Fabrica* we have the first adequate description of the structure of the body based upon actual observation. It has sometimes been asked what did Vesalius discover, since no organs of note were named for him. It may be said that in a sense he discovered the correct gross anatomy of the entire body, as there is no region that he did not illuminate by his observations. A few of the structures not previously mentioned by others, yet described by him, are the internal pterygoid and lingualis muscles, the inferior longitudinal sinus, the septum lucidum, the seminiferous ducts. Considering that he had not the aid of the microscope, it is remarkable how just an idea he obtained of the intimate structure of the liver, the kidney and the spleen. He did not trouble himself much with speculation, being content to record his own observations. In theory he was a Galenist. While corrections of Galen swarm on almost every page he evidently holds by the doctrine of the "spirits," though he does declare that the nerves are not hollow tubes.

It is not surprising that in such a herculean task as he performed he made some errors. He thought there was a fibrocartilage in the shoulder joint, that the spleen emptied a secretion into the stomach by the vasa brevia of the splenic artery, that the crystalline lens was in the middle of the eyeball, that the olfactory nerve conveyed air to the brain. Some of his errors were corrected during his lifetime by Fallopius and Eustachius.

You are aware of the tremendous controversy that the publication of the *Fabrica* raised, and that Vesalius, angered at the injustice shown him, shortly after publishing a second edition of the *Fabrica*, burned his manuscripts and retired to the Spanish court. He was proud, sensitive, impatient of opposition, indignant at abuse. He says in the letter on the China root, written in 1546, that he had been advised to moderate his attacks on Galen, but he cannot lie about what he has himself seen. It is the equivalent of Luther's "Ich kann nichts anders."

We know but little of the secret reasons that may have led him to abandon his work in the midst of what seems to us now a brilliant success. It is often alleged that it was the result of machinations of the theologians of the time. It was undoubtedly a great loss to science, for he was a pathmaker and proclaimer of truth, one who brought science back to rational observation. He was one of those who work—

"Each for the joy of the working, while each, in his  
separate star,

Shall draw the thing as he sees it, for the God of things  
as they are."

(Dr. Baker exhibited numerous lantern slides, showing cuts from the *Fabrica*, the great contrast between them and previous work and the influence they had on subsequent anatomical illustration. The anatomical drawings of Leonardo were also shown, and contrasted with the work of Vesalius.)

### 3. The Personality of Vesalius. DR. F. H. GARRISON.

Dr. Welch, in his inimitable, contrapuntal way, has shown the relation of Vesalius to all the cultural phases of the Renaissance period. Dr. Baker has made us see, from the actual illustrations,

how great a work the *Fabrica* is, and how Vesalius made anatomy a subject of equal importance with painting, sculpture, or any other branch of art or science. With the aid of Dr. Harvey Cushing's remarkable series of Vesalian portraits, which includes a number of paintings not listed by Roth, I hope to give some impression of the kind of man Vesalius was, using a few other pictures I have ventured to add to those which Dr. Cushing has kindly lent me. As we pass these Vesalian portraits in review, let us reflect that this great physician was not only the man who put scientific anatomy on its feet, and made it viable and respectable, but was, in his fiery youth, one of the protagonists of free thought, one of those to whom we owe such moral, intellectual and spiritual liberty as we have. He stood for the truth in science, that the truth, as he saw it, should be spoken.

Beginning with the wood engraving in the first imprint of the *Fabrica* (1543), we see a stocky burly figure, evidently of short stature, with shaggy hair and beard, a tip-tilted nose, suggesting native pugnacity and a satirical disposition, obviously a man full of pluck and courage; also a man of strife and contention, not given to brooking opposition, and inclined to make himself disagreeable to those who opposed him. "Hardly the sort of man," Dr. Fletcher used to say, "that one would care to have an argument with." The expression of the eyes in the *Fabrica* engraving is unprepossessing, as we shall see by comparison with the oil portraits. One point in this engraving is of special importance. We see Vesalius with an ink pot and manuscript before him, holding a dissected forearm, evidently engaged in jotting down his findings. This, with the splendid title-page of the *Fabrica*, tells us how much he respected his calling, that he was not above his business, no snob, in spite of his well-to-do origin, and that he used his strong personality and his social position to make his subject respected and honored by all men. Passing now to the Glasgow portrait by Calcar, which was once owned by William Hunter, we have the same pugnacious turned-up nose, and the combative, not very reassuring expression of the eyes, which are, however, uniformly dark, striking and expressive in these oil portraits, an expression which somehow indicates a disharmony, as of a not entirely happy man, with nothing of the serenity and repose which we see in such faces as those of Lister, Trousseau and Carl Ludwig, or in such anatomists as Sir Charles Bell and Henle, who were fascinating through their artistic talents, or Hyrtl and Oliver Wendell Holmes, who were beloved for native kindness, ready wit and good humor. In all the other portraits in Dr. Cushing's series, which I hope he will some day describe at length, there is a certain resemblance. The eyes in all these pictures remind us of Scotch faces we have seen, suggesting tenacity of purpose, readiness for argument, perhaps an excess of devotion to the intellectual side of things. These oil portraits indicate Vesalius' sense of his superior social position, that he was no mere scrub, to be thrust aside and trampled upon, but a man of the world, who had played his part in the larger life, "used to something," accustomed to have his own way and inclined to let people give the wall to his peculiarities. One who, as Dr. Cushing has said, was not the least bit afraid, a hard hitter, every inch of him a man. We can read these traits clearly, because these courageous, straightforward characters are inevitably open and above board, have nothing to hide, are not subtle or inscrutable. The defects of their qualities are that they are not clever, not gracious, not always considerate of others, and hence, since "the world an ancient murderer is," are in a way to set traps for their own undoing. The only fault which has been imputed against Vesalius is that, in 1544, he gave up his life-work, burned his manuscripts and became Court Physician to Charles V, perhaps in order to place himself beyond the reach of Sylvius, Columbus, and his other enemies, who would gladly have seen him haled before the Inquisition. At any rate, Servetus was burned in 1553,



and we cannot blame Vesalius if (his common sense coming to his aid), he said, "environment wins," and became suddenly worldly wise. But at what a cost! To live as a hanger-on of courts, sacrificing the work which was the very bread and wine of his mind and giving himself up to that complacency of creature comforts, the imputation of that worship of wealth, power and worldly place, in and for themselves, which is esteemed profoundly middle-class. In 1561, the old spirit is set aflame by the publication of the Anatomical Observations of Fallopius, and then—the pilgrimage to Zante and the end.

In Dr. Cushing's series of paintings of individuals resembling Vesalius, the Tintoretto in the Pinakothek (Munich), supposed to be Vesal, the portrait from the Louvre, and the Moro from the National Gallery (London), have all some points of resemblance. The portrait of a sculptor by the Venetian painter, Moroni, may be said to epitomize the Vesalian type of countenance, as seen in the Fabrica engraving. There is the same shaggy strength and sturdiness and the suggestion that the individual might be a dangerous one to cross. The Goya portrait, which I have ventured to add, representing General Juan Martin, surnamed "El Empeinado," a Spanish *conquistador*, possibly a cut-throat, like Spargacucile in "Rigoletto," may be said to suggest the Vesalian type of head with all the elements of good left out of it. A photograph of G. F. Fitzgerald, an eminent mathematical physicist of the Ulster school, who, like Vesalius gave up his life-work, but for the definite purpose of advancing the cause of education in Ireland, represents a face full of soul and fire. There is a similar expression in certain pictures of the anatomist Joseph Leidy, and we might imagine the countenance of Vesalius lighted up in the same way, when stirred by enthusiasm for his work. The Whistler portrait of Carlyle, a head which is Vesalian in contour, has some of the elliptical tendencies of the Impressionist School. There are gaps and blanks in the face and it is of this painting that a critic has said that the artist "has not told us one significant fact about his model, his nationality, his temperament, his rank, his manner of life." [Here a series of lantern-slides was introduced, representing women of different races—Italian, Spanish, Jewish, Servian, English, Irish, Scottish—each of highly specialized type, assimilating to a certain norm of facial beauty set by Titian. All are more or less alike, yet it would not be difficult to point out the differential characters of race in each; but nothing special could be predicated of the character, temperament or morale of the individuals represented because the type is ambiguous or undecipherable, appeals more to our sense of beauty than to our sense of character.] In the faces of men of letters and science, of rugged characteristics, whose lives have been as an open book, it is not so difficult to read some of their traits. In Carlyle, the resemblance to Vesalius is precisely in the contour of the head, particularly in the jutting, crag-like forehead and the short, blunt, obstinate nose of the Scotch country people. The photograph of 1860 gives us the Carlyle of tradition, gloomy, scornful, dyspeptic, unhappy, suggesting the memorable sentence in his diary: "The ground of my existence is as black as death."

All this is very unlike Vesalius, of the *grande bourgeoisie*, courted and honored by the great, yet with all of Carlyle's contrariness and whimsicality, there is, you will admit, a resemblance, in that the resolute, aggressive Vesalius, like Carlyle, stood out staunchly for his own subject, taught all the world of his time that scientific anatomy, like poetry, painting, sculpture, music, mathematics, physics, or the other fundamental branches of science, is a big subject, is, as Dr. Welch has said, the "foundation stone of scientific medicine."

In the dark eyes of Beethoven, as seen in Hornemann's miniature of 1802, there is a resemblance to some of the portraits of Dr. Cushing's collection, particularly in the extraordinary dilatation

of the pupil, upon which all biographers of Beethoven dwell. Beethoven, too, had the highest respect for his calling, in fact, was, with Händel, the first to make the musician and the composer respected in society.

What has all this to do with the personality of Vesalius? Well, first and foremost, Vesalius, a native of Brussels, his genius of the Germanic order, with the wonderful power of assimilating and coordinating knowledge, was, in every sense of the world, a cosmopolitan, a man of the world and a citizen of the world. While he does not belong to the sacred band of "prophets, transfigured saints and martyrs brave," like Servetus or More or Bruno or Lavoisier or Semmelweis, he had, in his ardent youth, something of the spirit of those who risk "their lives, their fortunes and their sacred honor" for the cause of truth, something of the Huxley type; in character, something of these blameless honorable lives. But he is of chief interest to us in that he used his commanding position to make anatomy a world subject like art or poetry or philosophy. We might define the Fabrica as a world anatomy, in the same sense that the Iliad, the Divina Commedia, Hamlet and Faust are world poems, or Beethoven's symphonies are world music. Byron and Walter Scott were hasty, careless writers, poor stylists, like Vesalius, yet they too took all Europe by storm as romantic poets and novelists, and for the same reason, namely that their work was not narrowly racial, national and local, but had in it elements which appeal to and are common to all mankind. And so, to borrow Lord Morley's eloquent words about Byron, the judgment of mankind, the *Securus judicat orbis terrarum*, has agreed to place Vesalius in "that band of far-shining men of whom Pericles declared the whole world to be the tomb."

#### List of Works of Vesalius Exhibited.

From the Surgeon General's Library (courtesy of Dr. F. H. Garrison):

Paraphrasis in nonum librum Rhazae, ad regem Almansorem de affectuum singularium corporis partium curatione. 10 p. l., 224 pp., 4 l., 16mo. (R. Winter, 1537.)

Epistola, rationem modumque propinandi radicis Chynae decocti . . . . pertractans: et praeter alia quaedam, epistolae cuiusdam ad Jacobum Sylvium sententiam recensens, veritatis ac potissimum humanae fabricae studiosis perutilem; quum qui hactenus in illa nimium Galeno creditum sit facile commonstret. 204 pp., 7 l., fol. (Basilae, ex officina Joannis Oporini, 1546.) Bound with Dantz (J) Universales Joannis Mesue canones. fol. (Basilae, 1545.)

From the library of Dr. Henry Barton Jacobs:

ANDREAE VESALII Invictissimi Caroli V. Imperatoris Medici OPERA OMNIA ANATOMICA & CHIRURGICA. Cura HERMANNI BOERHAAVE Medicinae, Botanices, Collegii Practici, & Chemiae in Academia Lugduno-Batava Professoris, & BERNHARDI SIEGFRIED ALBINI Anatomes & Chirurgiae in eadem Academia Professoris. Tomus Primus et Secundus. (Lugduni Batavorum. Joannem du Vivie et Joan & Herm. Verbeek, MDCCXXV.)

From the Howard A. Kelly Collection of The Johns Hopkins Hospital Library:

Andreae Vesalii Bruxellensis, scholae medicorum Patuinae professoris, de Humani corporis fabrica. 7 l., 663 pp. (Basileae, Joannis Oporini, 1543.)

Von des menschen cörpers Anatomey, ein kurzer, aber vast-nützer ausszug, auss D. Andree Vesalij von Brussel bücheren, von ihm selbs in Latein beschriben, unnd durch D. Albanum Torinum verdolmerscht. fol. (Basel, Johann Herpst, 1544.)



De Humani corporis fabrica. Epitome: cum annotationibus Nicolai Fontani, Amstelredamsis medici. fol., 112 pp. (Amstelodami, apud Joannem Janssonum, 1642.)

Epistola, rationem modumque, propinandi radicis Chynae decocti . . . pertractens: et praeter alia quaedam, epistolae cuiusdam ad Jacobum Sylvium sententiam recensens, veritatis ac potissimum humanae fabricae studiosis perutilem; quum qui hactenus in illa nimium Galeno creditum sit facile commonstret. 16mo. 100 pp. (Venetiis, 1546.)

## THE LAENNEC.

FEBRUARY 24, 1915.

1. \* Early Diagnosis of Pulmonary Tuberculosis. DR. L. HAMMAN.
2. \* The Results of Inducing Pneumothorax in Pulmonary Tuberculosis. DR. M. F. SLOANE.
3. \* The Occurrence of Tubercle Bacilli in the Circulating Blood. DR. C. R. AUSTRIAN.
4. \* Results of Sanatorium Treatment. DR. S. WOLMAN.

\* To appear later in the BULLETIN.

## NOTES ON NEW BOOKS.

*Skin Diseases in General Practice.* By HOLDIN DAVIS. (London: Henry Frowde and Hodder & Stoughton, 1913.)

The chief reason the author gives for publishing this book is that so few text-books on the subject are sufficiently practical for general use. It is undoubtedly true that the arrangement of most text-books presupposes some knowledge of skin diseases, and that no practical method is given for making diagnoses, although some works on dermatology have tried to correct the latter fault by introducing a chapter on regional distribution, in which are listed the diseases that attack any given locality.

This work by Dr. Davis is simply an elaboration of this scheme. But although this is truly a step in the right direction, many difficulties must be overcome before such an arrangement can be considered ideal. That there must be endless repetition the author quickly discovered, and endeavored to correct by describing, according to the older method which he decried, three groups of diseases, viz.: those due to pyogenic cocci, eczema and syphilis. After these come the chapters on the diseases attacking various regions. While one can appreciate the reasons for describing eczema and syphilis separately, there are other diseases that, from their arrangement, distribution, etc., present more difficulties in the way of diagnosis than those due to pyogenic cocci.

To make such a classification as this most practical, there must be added other descriptive details, and it is probable that it would enhance the value of such a scheme if, instead of merely listing the various diseases, they should be grouped according to their chief objective symptom, whether erythematous, papular, vesicular, pustular, scaly or crushed.

The book is written in a conversational manner, which makes it decidedly attractive. The descriptions of the various diseases are accurate and sufficiently complete, though we must take exception to the statements that impetigo never occurs as a solitary lesion, and that it is the commonest skin disease. One also notices a number of anomalous arrangements, such as grouping both forms of sycosis under furunculosis; calling a dermatitis due to external irritants dermatitis traumatica; describing dysidrosis under eczema; grouping lichen planus with erythema multiforme, urticaria, etc., as an eruption of toxic origin; calling lichen chronica simplex a circumscribed prurigo, and others.

Treatment is described in a simple but satisfactory manner and a special chapter is given to "Some Modern Methods of Treatment."

The illustrations are fairly numerous and well selected, but not very clear.

*Infection and Resistance.* By HANS ZINSSER. \$3.50. (New York: Macmillan Company, 1914.)

An admirable book—a treatise the equal of any of its kind. The author has treated a complex and technical subject with such clarity and in so charming a manner that the labyrinthine reasonings of this branch of medical science seem easy and direct.

In developing each of the topics dealt with, the author carries the reader through the evolution of knowledge of the subject in

hand; the steps needed for the solution of problems are indicated, the researches that led to the finding of these solutions abstracted and the conclusions arrived at detailed. Where discussions have arisen the two or more aspects of the controversy are presented and the authority for the several views is quoted. The knowledge of the more recently studied phases of immunity is carefully analysed and judiciously set forth. This is especially true of the chapters on anaphylaxis and vaccine therapy.

From the happy choice of the title through the excellent chapter on Colloids, by Dr. Stewart Young, one is favorably impressed with the book. It is a work that satisfies a need, for it places in the hands of those interested a clear, comprehensive, critical and authoritative digest of a most important subject. The bibliography is extensive, the index ample, and except for a few minor typographical errors, such as the misplacing of a decimal point in several of the tables (pages 107, 207), the use of "titrated" for citrated, on page 442, and a few equally trivial mistakes, no criticisms seem in order.

*Poverty and Tuberculosis: The Home Hospital Experiment, 1912-14.* Published by the New York Association for Improving the Condition of the Poor, 105 E. 22d street, New York City. Publication No. 84.

This booklet contains the result of two years of the Home Hospital experiment, and the work done demonstrates three things:

1. It is possible to treat families in which one or more members are afflicted with tuberculosis, by keeping the family together, in their own individual home, without danger to other members of the family.

2. The results of training patients in their own homes under satisfactory conditions of living, with adequate medical supervision, compare favorably with results secured by removing the patient from his home and treating him in a sanatorium or other special institution for tuberculosis.

3. In the case of a family in which there are combined tuberculosis and poverty, care of the family as a unit by the Home Hospital method costs less than to break up the family, as is done under other methods of treating families with tuberculosis.

Modern methods of treatment recognize the psychological factor in the care of all patients and especially so in those suffering from tuberculosis. Take a man or woman away from home and family, and there is then the worry about the family added to that incidental to the disease. But if the treatment can be carried on at home, the mental attitude, rather than retarding, aids in the cure.

The Home Hospital is a large, clean apartment house, each apartment consisting of from two to four rooms, and provided with a sleeping porch. A roof garden has a solarium for patients "taking the cure." The general scheme of the building is to provide the maximum amount of fresh air and sunlight. In this building are over two hundred individuals, 130 of whom are patients, this being one-half as many patients as are in the New York or Presby-



terian Hospital. The average number of patients is greater than at the Trudeau Sanatorium at Saranac Lake, N. Y.

The Home Hospital idea is that of a decently constructed house, with a decent budget available to provide adequate nourishment, together with provision for constant medical and nursing supervision of the family; and it would seem that, given these, the spread of tuberculosis can practically be prevented.

The reader will be impressed with the fact that the Home Hospital is treating not only tuberculosis, but all cases of sickness occurring in the families, and advising them in hygiene, so that the resistance of all the individuals may be raised and thus sickness be prevented.

Furthermore, the supervision is more than medical; it is moral also.

The paper is exceedingly interesting. This is the first experiment along such lines; the work has been done systematically and careful records have been made. The results are appended in tables and the whole report is of great value.

*Immunity.* By JULIUS CITRON. Translated from the Second German Edition by A. L. GABBAT. \$3.50. (Philadelphia: P. Blakiston's Son & Co., 1914.)

The popularity of this really excellent book is shown by the appearance of a second American edition within a year of the first translation. There are numerous additions and alterations which bring the work well up to date. These have been made in part by the editor, who has incorporated some of the more recent American work not covered in the German edition.

The book is not a text-book in the ordinary sense, but is designed as a compact and practical manual for the laboratory worker and for the clinician with some laboratory training. Detailed directions are given for carrying out, by the most approved methods, all the ordinary procedures of serum diagnosis. Special emphasis is placed on the possible sources of error and the control tests necessary to exclude them. The general principles and theories on which the tests are based also receive brief consideration.

The book will also be useful to the clinician in showing how these tests may be applied in practical diagnosis. Their limitations are pointed out and, as a rule, a commendable conservative attitude is maintained in discussing their reliability. The book contains an excellent chapter on tuberculin in diagnosis and treatment, as well as brief discussions of vaccine and serum therapy.

*Progressive Medicine: A Quarterly Digest of Advances, Discoveries and Improvements in the Medical and Surgical Sciences.* Edited by HOBART AMORY HARE, M. D., Philadelphia, assisted by LEIGHTON F. APPLEMAN, M. D., Philadelphia. Volume IV. December, 1914.

Diseases of the Digestive Tract and Allied Organs, the Liver, Pancreas and Peritoneum—Diseases of the Kidneys—Genito-Urinary Diseases—Surgery of the Extremities, Shock Anæsthesia, Infections, Fractures and Dislocations, and Tumors. Practical Therapeutic Referendum. (Philadelphia and New York: Lea & Febiger, 1914.)

In reading this quarterly digest of medical and surgical progress one is impressed by the immense range of literature covered by the various papers. Thus in surgery alone, including genito-urinary surgery, we find 175 out of a total of 405 pages; and yet hardly more than half a dozen topics have been touched upon. In elaborateness and thoroughness of treatment, although possibly not in literary form, many of the sections resemble the "Analytical and Critical Review," which filled such an important place in the English medical journals of a half century or more ago. It

is interesting to observe that the newest literature is not only gathered together, but also carefully discussed and subjected to criticism. The need of such an assemblage and comparison of facts from widely different sources is well illustrated by Bloodgood's treatment of surgical shock in the volume before us. It is to be regretted that, like everyone else who has written upon the subject, he finds it easier to commend the methods adopted by surgeons to relieve shock than to explain its causation.

The section on therapeutics, under the rather pretentious title "Practical Therapeutic Referendum," is of equal value. It is not practicable to mention in detail the remaining sections of this excellent work. They are all real contributions to their respective branches of medicine and deserve a wide reading.

*A Text-Book of Pathology for Students of Medicine.* By J. GEORGE ADAMI, M. A., M. D., F. R. S., Strathcona Professor of Pathology, McGill University, and Advisory Pathologist to the Montreal General and the Royal Victoria Hospitals, Montreal, Canada; late Fellow of Jesus College, Cambridge, England; and JOHN McCRAE, M. D., M. R. C. P. (Lond.), Lecturer in Pathology and Clinical Medicine, McGill University, Montreal; Senior Assistant Physician, Royal Victoria Hospital; Sometime Professor of Pathology, University of Vermont; late Fellow of Biology, University of Toronto, Toronto, Canada. Second edition, revised and enlarged. Illustrated with 395 engravings and 13 colored plates. (Philadelphia and New York: Lea & Febiger, 1914.)

We must agree with the authors "that the first edition of this text-book has measurably succeeded in its purpose is inferable from the early exhaustion of the large first edition." The second edition continues the same high standard which the authors reached in its predecessor. The orderly arrangement of the subject matter, the careful classification and correlation of the many facts, and their clear and concise presentation, particularly adapt the volume to its intended and entitled purpose. The aim of the authors to emphasize the reasons underlying pathological conditions is more than justified, since the ability to recognize individual pathological phenomena must, in great measure, be derived from actual experience. The changes in this edition are numerous. The syllabus at the head of each chapter is quite appropriate and most convenient. There is a new chapter on the more important infections. The chapter on monstrosities has been relegated to the appendix. There are a number of new illustrations. All these are decided improvements with the one possible exception, the change in nomenclature of tumors.

The book may be heartily recommended to students of pathology.

*Practical Sanitation.* A Handbook for Health Officers and Practitioners of Medicine. By FLETCHER GARDNER, M. D., and JAMES PERSONS SIMONDS, B. A., M. D. \$4 net. (St. Louis: C. V. Moseley Company, 1914.)

This little publication by Gardner and Simonds contains a mass of information regarding sanitation, systematically arranged and of great value to health officers and physicians. The practical experience of the authors has shown the necessity of disseminating information of this character and "Practical Sanitation" deserves a wide circulation and a careful perusal by medical men.

## ERRATUM.

February, 1915. The Recognition of Atypical Forms of Intestinal Amœbiasis. SELLARDS, A. W., and BAETJER, W. A. Page 45, Outline, IV, 3, for *E. limax* read *limax*.



Mathist

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# BULLETIN

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# TWENTY-FIFTH ANNIVERSARY OF THE JOHNS HOPKINS HOSPITAL 1889-1914.

## PAPERS, CLINICS AND DEMONSTRATIONS ILLUSTRATING THE WORK OF THE HOSPITAL IN MEDICINE, SURGERY, GYNECOLOGY, OBSTET- RICS, PSYCHIATRY, UROLOGY, PATHOLOGY AND NURSING.

### INTRODUCTION.

In presenting the papers which were read in connection with the celebration of the Twenty-Fifth Anniversary of the Opening of the Hospital, it seems appropriate to precede the papers with a brief account of the exercises of the week.

The gathering of former members of the House Staff, of graduates of the Department of Medicine of The Johns Hopkins University and of graduates of the Training School for Nurses connected with the hospital, was unusually large, in view of the fact that the recent outbreak of general war in Europe and the great uncertainty of the future of business in the United States and Canada had kept many away.

Upon Monday morning, October 5, the graduates of the Training School for Nurses met in the Assembly Room of the Henry Phipps Psychiatric Clinic, when the following papers were presented:

By Miss Effie J. Taylor, "Nursing in the Henry Phipps Psychiatric Clinic."

By Miss Margaret S. Brogden, "Hospital Social Service."

And by Miss Mary E. Lent, "The Visiting Nurses of Baltimore."

In the afternoon the opening meeting occurred at The Lyric. The exercises and papers presented at this time were published in the December number of the BULLETIN.

In the evening a dinner for former residents of The Johns Hopkins Hospital and invited guests was given at the Belvedere Hotel.

Upon Tuesday the following program was presented by former members of the House Staff of the Medical Department:

By Dr. George Blumer, Dean of the Medical Department of Yale University, New Haven, "The Medical Treatment of Peptic Ulcer with Especial Reference to the Lenhartz Treatment."

By Dr. Thomas McCrae, Professor of Medicine at the Jefferson Medical College, "Tertiary Syphilis of the Liver."

By Dr. Richard P. Strong, Professor of Tropical Medicine, Harvard University, "Recent Developments in Relation to the Study of Tropical Medicine in the United States."

By Dr. Charles P. Emerson, Dean of the Indiana University Medical School and Professor of Medicine in Indiana University, "The Nervous Patient."

By Dr. Peyton Rous, Research Worker, Rockefeller Institute for Clinical Research, "The Influence of Dieting upon the Course of Cancer."

By Dr. Campbell P. Howard, Professor of Medicine, University of Iowa, "The Diagnosis of Mediastinitis."

And by Dr. Douglas VanderHoof, Professor of Medicine, Medical College of Virginia, Richmond, Va., "The Causes of Indigestion—A Study of 1000 Cases."

At the same time in the Gynecological Department, the following papers were presented:

By Dr. John G. Clark, Professor of Gynecology in the University of Pennsylvania, "Ultimate Results from Surgery in Cholelithiasis."

By Dr. Curtis F. Burnam, Associate in Gynecology at The Johns Hopkins University, "A Brief Outline of the Status of Radium Therapeutics."

By Mr. Max Brödel, Professor of Art in Medicine, Johns Hopkins University, "Origin, Growth and Future of Medical Illustration at The Johns Hopkins Medical School."

At 12 noon, demonstrations and clinics were given in the Obstetrical Department.

At 1 p. m. a luncheon was given to the Medical Alumni in the Officers' Dining-room.

A luncheon was also given to the wives of visiting members at the Baltimore Country Club by a committee of Baltimore ladies.

At 2.30 p. m. an inspection was made of the Harriet Lane Home for Invalid Children, under the direction of Dr. John Howland.

Also at 2.30 p. m. the following papers were presented in the lecture room of the Psychiatric Department of the Henry Phipps Clinic:

By Dr. August Hoch, Director of the State Psychiatric Institute of New York, "A Study of the Benign Psychoses."

By Dr. John T. MacCurdy, Associate in the State Psychiatric Institute, Ward's Island, "Ethical Aspects of Psychoanalysis."

By Dr. Stewart Paton, of Princeton University, "Observations on Embryo Guinea-pigs."

By Dr. Charles S. Ricksher, Clinical Director of the State Psychopathic Institute, Kankakee, Ill., "The Onset of General Paralysis."

By Dr. Wm. Burgess Cornell, Executive Secretary, "Extramural Psychiatry in Baltimore."

At 4.30 p. m. a garden party was given upon the hospital lawn.

In the evening a dinner was given by the Medical Alumni at the Belvedere Hotel.

Upon Wednesday at 9.30 a. m., in the Surgical Amphitheater, papers and demonstrations were given by Drs. Halsted, Finney, Bloodgood, Mitchell, Churchman, Cushing and Heuer. These were not reported nor in any instance committed to writing, and consequently cannot be printed.

At 11 a. m., in the Urological Department, the following papers on urological surgery were presented:



By Dr. H. H. Young, "Organization of the Urological Institute."

By Dr. Frank Hinman, "Preparatory Treatment of Urological Operations."

By Dr. David M. Davis, "The Significance of the Distribution of Urea in the Human Body."

By Dr. John T. Geraghty, "Renal Functional Tests."

And by Dr. Norman M. Keith, "Experimental Hydronephrosis."

At 1 p. m. a luncheon was given in the roof garden of the Henry Phipps Psychiatric Clinic, to the Alumni of the Medical School and their wives, and the Alumnae of the Training School for Nurses.

This was followed by visits to the laboratories in pharmacology, physiology and anatomy.

In the evening there were class dinners for the Alumni of the Medical School and for the Alumnae of the Training School for Nurses at the Belvedere.

Upon Thursday, at 9.30 a. m., former members of the Patho-

logical Department gathered in the Medical Amphitheater and the following papers were presented:

By Dr. Simon Flexner, Director of the Rockefeller Institute for Medical Research, "The Microbic Cause of Poliomyelitis."

By Dr. William G. MacCallum, Professor of Pathology, Columbia University, "The Bone Changes in Chondrodystrophia."

By Dr. Charles H. Bunting, Professor of Pathology, the University of Wisconsin, "Diphtheroid Infections."

And by Dr. William T. Howard, Late Professor of Pathology in Western Reserve University, "Syncytium Formation in Tumors." \*

At 1 p. m. a luncheon was given by Dr. H. H. Young to the Medical Alumni and others in the new James Buchanan Brady Urological Institute, which was followed by an inspection of the Institute.

At 4.30 p. m. on Tuesday, Thursday and Friday, the first, second and third lectures on the Herter Foundation were given by Dr. Lewis, of University College, London.

\* No copy of this paper has been furnished for publication.

## MEDICINE.

### THE MEDICAL TREATMENT OF PEPTIC ULCER WITH ESPECIAL REFERENCE TO THE LENHARTZ TREATMENT.

By GEORGE BLUMER, M. D.

The question of the most efficient medical treatment for those patients with peptic ulcer who properly come under the care of the internist cannot be said to be definitely settled. There is a fairly substantial agreement that patients suffering from certain types of peptic ulcer should undergo surgical rather than medical treatment, and even internists would nowadays hardly agree with Minkowski's dictum, "that every case of gastric ulcer should be treated medically once." Ulcer patients with acute perforation, those with pyloric obstruction even in the early stages, those suffering from the results of repeated small hemorrhages intractable to medical treatment, and those with subphrenic abscess, hour-glass stomach, or serious perigastric adhesions, had all best pass into the hands of a competent surgeon without delay. On the other hand, the great majority of patients with hemorrhage of the fulminating type, those with acute ulcers, and those with uncomplicated chronic ulcers, should certainly have the benefit of a carefully regulated and supervised medical regimen before being submitted to the knife. This is the case in the group last mentioned, notwithstanding the one great drawback common to all forms of medical treatment, the long duration of the cure.

The regimens now in use in the treatment of peptic ulcer have certain essential features in common, such as absolute rest, the use of certain accessory medicaments, external applications of heat or cold to the epigastrium, and certain principles regarding the care of the bowels. It is true that universal agreement as to the period of absolute rest, the efficiency of

bismuth or the alkalies, and the desirability or undesirability of forcing the bowel movements during the first week after hemorrhage does not exist, but it is fair to state that there is substantial agreement on these points. The contrast between the different systems lies essentially in differences in the diet, and it is from the dietetic point of view that they are best compared. A classification based upon very strict dietetic grounds is, however, hardly possible, as all of the prevailing types of diet have submitted in the hands of others than their originators to more or less considerable modifications, and these have resulted in overlapping. Three fairly sharply defined groups of diets can, however, be recognized; one in which more or less complete abstention from mouth feeding is the predominant feature, typified by the Leube cure; one in which immediate feeding with albuminous food is the essential peculiarity, typified by the Lenhartz diet; and one in which fats constitute the important source of nourishment, typified by the diets of Strauss and Jarotsky. The diet of Loeper, in which sugar constitutes the sole nutritive element, is not comparable with those already mentioned as it is a temporary diet for a certain type of case, namely, the patient with the so-called "irritable" ulcer.

The regimen of v. Leube<sup>1</sup> is the lineal descendant of the milk diets of Cruveilhier and v. Ziemssen. The essential features of the cure are: Rest in bed; the daily use of luke-

<sup>1</sup> Full details of the different regimens will be found in the appendix.



warm Carlsbad water; the application of hot poultices and Priessnitz compresses to the epigastrium; and a diet mainly of milk in increasing quantities, fortified after 10 days by the addition of cereals and finally by meat. In bleeding ulcers the diet is preceded by one to three days of starvation, with nutrient enemata, an ice bag to the epigastrium, and adrenalin, bismuth, and morphine medication. The principle underlying this diet is that to encourage healing of the ulcer the stomach must be spared from work as much as possible, and that in bleeding ulcers the organ must be given complete rest for a time.

Modifications of the Leube diet have taken two opposite directions. On the one hand, we find starvation as a means of resting the stomach carried to extremes in the regimen advocated by Rolleston, Wynter, and others of the English school of clinicians who give the patient no nourishment at all for periods of 10 days or longer; on the other hand, we find diets like those of Einhorn, Albu, and Boas, which increase the caloric value of the Leube diet by the addition to it of easily digestible and non-irritating nutriment.

The essential features of the Lenhartz regimen consists of absolute rest in bed for at least three weeks, an ice bag to the epigastrium until no occult blood appears in the feces, the routine administration of bismuth in all patients and of soft Bland pills in anæmic patients, and a non-irritating and non-stimulating diet of concentrated albuminous food given by the mouth from the onset of treatment and gradually increased in caloric value. The principles underlying this diet are: First, that hyperacidity plays an important role in preventing healing and that free acid must be neutralized by acid-binding food; and, second, that the general nutrition must be maintained and anæmia must be combated to favor healing of the ulcer.

Diets which depart to a greater or less degree from the Lenhartz diet have appeared since Lenhartz first proposed his regimen in 1901. In this country slight modifications, which make the diet more suited to American tastes, have been proposed by Samuel W. Lambert and others. In England, the diet of Hort, though proposed on different theoretical grounds, is a concentrated albuminous diet and best classed in the Lenhartz group. Senator agrees with Lenhartz regarding the advisability of introducing nourishment into the stomach early in the treatment, and regarding the neutralization of hydrochloric acid as an important part of the treatment. His diet aims to neutralize the acid by means of fats and sugars as well as proteins, and he also adds gelatinous substances both for their nutritive and hemostatic qualities. A good many German clinicians use the Lenhartz diet in patients with bleeding ulcers after a few days of starvation with rectal alimentation, a regimen which was suggested by Friedrich Mueller in the discussion on Lenhartz's paper at the German Congress of Internists in 1909.

Two diets which have apparently not been widely used, and which are based on the high caloric value of fats and their power to inhibit gastric secretion, are those of Jarotsky and Strauss. Jarotsky's diet consists of white of egg and olive

oil given separately, several hours apart, in increasing daily doses. Strauss uses a mixture of cream and yolk of egg either beaten up with sugar or rubbed up with butter.

All of the diets outlined above have their advocates, and all their opponents, and it cannot be denied that each has advantages and drawbacks that must be recognized if we are to intelligently treat our ulcer patients. The advantages are usually fairly obvious, the objections may with profit be discussed at some length.

The objections which have been urged against the Leube diet seem partly based upon general impressions and partly on statistics. Lenhartz, for example, says that frequent recurrences occur after this regimen, but as frequent recurrences occur after all forms of medical treatment, and as there is no large series of statistics covering this point, his statement loses force. The usual objections to the Leube cure may be briefly sketched as follows: The routine is prolonged and tedious; in bleeding cases the stomach is not completely at rest as there is hunger peristalsis and the nutrient enemata excite gastric movement; that gastric juice may be secreted even by the empty stomach; that undernourishment and even acidosis may occur, and that the former militates against the healing of the ulcer; that there is difficulty in keeping the mouth clean; that annoying vomiting may occur; that the nutrient enemata contain very little nourishment, are dirty, time-consuming, and cannot be used in the homes of the poorer classes unless trained nursing is available; that the milk over-distends the stomach and increases the pain. When the strenuous starvation of the English school is used, new terrors are added, thirst, and a tendency to parotitis which, when it develops, may prove fatal.

It is only fair to say that while there is undoubtedly truth in some of this formidable list of objections, many have been answered by Leube and his adherents. The best answer lies in Leube's record of a mortality of only 2.5 per cent in patients with bleeding ulcers, and 90 per cent of immediate recoveries in all types of cases. That a routine is prolonged and tedious is not a serious objection if it results in the cure of a much more prolonged and tedious disease. If the empty stomach is not completely at rest, it is surely as fully at rest as one into which food is being introduced every hour. The undernourishment occurring in the Leube cure is not as a rule severe, and 42 per cent of the patients actually gain weight. Annoying vomiting may occur in some patients under any regimen, and nutrient enemata are now universally recognized as at best a temporary expedient which is, however, from 400 to 1000 calories per day better than no nourishment at all. That 250 cubic centimeters of milk, the maximum dose under the Leube cure, should distend an organ capable of holding two liters seems open to doubt.

The objections to the Lenhartz cure have been almost as numerous as those urged against the Leube regimen. Many clinicians strongly object to the immediate feeding of patients with bleeding ulcers, though fairly extensive comparative figures of the Leube and Lenhartz cures show that fewer recurrences of the bleeding during treatment occur with the Len-



hartz than with the Leube cure. The objection is frequently made that in some patients the smallest quantity of food causes severe vomiting, and this is undoubtedly true in the so-called irritable ulcers. Objection to the raw eggs on the part of patients is stated to be not uncommon, and the milk and raw meat are also cited as causes of distress and distention. Several object to the administration of meat as early as the sixth day, and frequent criticisms of the Bland pills on the ground of gastric irritation are found in the literature. As in Leube's case, Lenhartz's best answer to these criticisms is a mortality of 2.3 per cent in bleeding cases, and 90 per cent of patients with immediate relief. Doubtless all of the objections raised have been true of individual patients, but (and this is true of objections to any recognized routine treatment) they are not generally true.

The one great objection to the fat cures (Strauss, Jarotsky), and to a lesser extent to the Senator cure, which contains a good deal of fat, is the inability of most patients to tolerate the large quantities of fat which they contain. This intolerance is quite widespread among the inhabitants of temperate climates, and doubtless accounts for the fact that the fat regimens, theoretically so desirable, have not been more widely used. Even the advocates of fatty dietaries recognize their limitations, but, as one would expect, they fail to emphasize them as forcibly as impartial observers.

The results obtained by these different regimens are difficult to compare for several reasons. But few observers are able to present reports of series of cases large enough to give confidence in their statistical value. No figures are available which adequately cover the remote effects of the different treatments. The value of statistics in ulcer cases, especially statistics covering small groups, is more or less invalidated by the great variations in the natural history of the disease, and by the fact that it is impossible in any series medically treated to be sure that the diagnosis was always correct. Some of the large series of statistics are undoubtedly of value and may be briefly summarized. Leube treated 627 patients with a total mortality of 0.3 per cent, and a mortality in bleeding cases of 2.5 per cent. Only 1 per cent of his patients showed no improvement under treatment, and 90 per cent showed complete relief of symptoms on their discharge. Lenhartz's 295 patients were all subjects of bleeding ulcer, and both his subjective cures and his mortality (2.3 per cent) are almost identical with the results of Leube. Figures covering surgical treatment are available but cover such a different type of cases that they are not fairly comparable. No other large series covering mortality and subjective cure under medical conditions seems to be published.

Our experience with the Lenhartz diet in New Haven<sup>2</sup> covers 27 cases treated by that diet with unessential modifications. I feel that while the number of patients treated is too small to allow us to draw any statistical conclusions of value, it is allowable to record certain definite impressions which we

have received. In general, it may be said that the Lenhartz diet is, as a rule, eminently satisfactory from the patient's point of view. The pain accompanying the disease usually disappears within a few days, and we can substantiate the claim of Lenhartz that narcotics are seldom necessary. The patients seldom complain spontaneously of hunger, though, when questioned, they sometimes admit its presence. Most patients lose weight during the first week or 10 days, but many of them regain it before the cure is ended, and some considerably surpass their weight on entrance, when discharged. In patients followed after discharge, great gains in weight are sometimes noted, as much as 30 pounds in one patient.

In none of the published statistics can I find any distinction between gastric and duodenal ulcers as regards the efficacy of the Lenhartz cure. Thirteen of our patients were suffering from the symptoms of duodenal rather than gastric ulcer, and 10 of these were entirely free from symptoms or signs of the disease at the end of treatment. All were benefited, there being no absolute failures. Five of them have remained well over a year and a half. In only one of those apparently cured have we a report of a relapse, and this occurred after eight months. This is a decidedly better record than is shown by our 14 gastric cases, two of which were absolutely unbenefited, one of them after two treatments, and four of which relapsed, three after short periods. While it is hazardous to draw conclusions from such small numbers of patients, I cannot help feeling that patients with gastric ulcers do less well on the Lenhartz diet than those with duodenal ulcers, and that this is due to the element of stasis being much more prominent in certain stomach ulcers, even when actual pyloric stenosis is absent.

Our experience with the Lenhartz diet also allows us to substantiate some of the objections made to it. In several instances, patients were unable to tolerate the raw egg diet, even when the eggs and milk were mixed. In some instances this was due to the fact that cold storage eggs were the only ones available at the time, rather than to any intrinsic objection to the egg as an article of food. This is, nevertheless, a real objection in patients with sensitive palates. In one or two instances the milk in the diet disagreed and had to be discontinued. In both the case of the eggs and that of the milk, the disagreement took the form of vomiting, often accompanied with a temporary return of pain. The raw meat of the original diet we did not employ, but substituted minced chicken, as suggested by Lambert. American observers, Gilbride for example, have noticed that the American stomach is intolerant to the raw meat and ham of the original Lenhartz regimen. We have on two occasions noted a return of hemorrhage during treatment, though this was not serious. We would also point out that a gain in weight is by no means always to be expected, and that while pain usually disappears early, tenderness remains much longer and is often present well along in the cure.

A critical study of the literature of the medical treatment of peptic ulcer, particularly the rest and diet cures, suggests

<sup>2</sup> The cases occurred in the service of my confrère, Dr. Tileston, and myself in the New Haven Hospital, or were seen in consultation.



certain conclusions. It seems safe to assume that certain types of peptic ulcer show a strong natural tendency to heal if given a fair chance. Ulcers near the pylorus tend to heal badly, while bleeding ulcers, for reasons not entirely clear, seem to heal unusually well. Many ulcers would doubtless heal on the all-important complete rest, plus any of the dietary regimens that have been discussed. Others would equally certainly fail to heal under any form of medical treatment. Originators of diets are apt to adhere too closely to those diets, and tend to become prejudiced against different, but equally efficacious ones. The practitioner, whose sole purpose is to cure his patients, and who need not be distracted from this by attempts to glorify the products of his own cortical cells, should realize that there are good points in all of the diets presented. Each has its advantages and each its drawbacks, and the wise physician is he who will use them as frameworks to be clothed with a dietary structure suitable to the needs of each individual patient.

## APPENDIX.

## THE VON LEUBE REGIMEN.

1. Absolute rest in bed one to two weeks; in the average case, 10 days. From the 11th day on for a period of several weeks, the patient must rest one to two hours after the principal meals.

2. One-quarter liter of lukewarm Carlsbad water  $\frac{1}{2}$  hour after breakfast for the first four weeks.

3. Hot flaxseed poultices to the epigastrium, changed every 10 to 15 minutes, and kept on from 8 a. m. to 8 p. m. Before applying the poultices, the skin should be thoroughly cleansed, and a borax-wax ointment should be applied. From 8 p. m. to 8 a. m., a Priessnitz compress is applied instead of the flaxseed poultice. If blisters form, which is not uncommon from the third to the tenth day, empty, wash with ether, dust with dermatol. Poultices must only be used if there has been no history of bleeding for three months.

4. The following diet in the form of three main meals and two accessory meals daily. The food must be measured accurately, and never more than 250 cubic centimeters of milk given at a feeding.

First 10 days, cooked milk, meat juice once a day, bouillon, softened Zwiebach, and cakes not sweetened. Two pieces of Zwiebach and four cakes allowed daily.

From 11th to 17th day, the first diet, plus mucilaginous soups, rice and sago cooked soft in milk, with beaten-up egg. Soft-boiled and raw eggs, calves' brains, and young chicken and pigeon.

From 18th to 22d day, well-cooked calves' feet, thin sliced raw ham, thin sliced rare beefsteak, mashed potatoes, bouillon containing mashed rice, a little coffee and tea.

From 23d to 30th day, lean roast beef, underdone broiled chicken and pigeon without sauce, venison and partridge which have hung until tender, macaroni, cut-up noodles beaten through a sieve, and a little white bread.

From the 5th week on, cold veal or pike, light souffles and desserts of rice, sago, and maizena, and one to two glasses of a pure wine are allowed.

Patients with bleeding ulcers have:

1. An ice bag to the epigastrium.
2. Complete starvation for from one to three days.
3. During the period of starvation, nutrient enemata.

4. No cathartic should be given to these patients during the first week.
5. Adrenalin, bismuth and morphine medication.
6. After the period of starvation, the regular regimen.

## ALBU'S DIET.

- 8 a. m.,  $\frac{1}{4}$  liter milk.  
 10 a. m., one egg, soft-boiled or beaten with sugar.  
 12 midday, one plate of rice thoroughly boiled in milk, or a puree of grits or oatmeal with cream and sugar.  
 2 p. m., one plate of thick bean or sago soup, strained, with butter and the yolk of one egg.  
 4 p. m.,  $\frac{1}{4}$  liter milk or cream, with two teaspoonfuls of Odda or Hygiama.  
 6 p. m., one soft-boiled egg with 10 grams of butter.  
 7.30 p. m., one plate of strained tapioca with milk, or an omelette souffle made with two eggs.  
 9.30 p. m.,  $\frac{1}{4}$  liter milk.  
 Caloric value of diet, 1500.

This diet is given for the first week. After this, the number of eggs is doubled. After three weeks, calves' foot or chicken jelly, finely chopped beef, lightly cooked, minced ham, and bread and butter is allowed. Patients are kept on this diet for several weeks and are kept in bed from eight to ten days.

## EINHORN'S DIET.

In bleeding cases, rectal feeding from three to five days, with small quantities of cracked ice and gelatin by mouth. After bleeding is over, or in non-bleeding cases, the following diet:

First three days. Hourly feeding from 7 a. m. to 9 p. m., inclusive. At each feeding, 150 cubic centimeters of milk, except at the following hours: At 10 a. m., milk and strained barley; at 1 p. m., 150 cubic centimeters of bouillon alone, or with the addition of 1 to 2 drams of peptone; at 5 p. m., strained barley or oatmeal is added to the milk again.

4th to 10th day. Feeding every two hours from 7 a. m. to 9 p. m. 300 cubic centimeters of milk are given at a dose. At 11 a. m. and 7 p. m., strained barley, rice, or oatmeal are added. At 1 p. m., 200 cubic centimeters of bouillon into which an egg is beaten, is substituted for the milk.

11th to 14th day. Feeding every two hours from 7 a. m. to 9 p. m. The milk is the basic ration in a dose of 300 cubic centimeters. At 9 a. m. and 5 p. m., two softened crackers are added to the milk. At 11 a. m. and 7 p. m., strained barley, rice, or oatmeal gruel. At 1 p. m., 200 cubic centimeters of bouillon with an egg beaten into it and two crackers take the place of the milk.

14th to 17th day. Feeding every two hours from 7 a. m. to 9 p. m. Basic ration, 300 cubic centimeters of milk, to which are added at 9 a. m., two crackers; at 11 a. m., barley, rice, or oatmeal gruel; at 5 p. m., one soft egg and two crackers; and at 7 p. m., farina. At 1 o'clock, 50 grams of scraped meat and 200 cubic centimeters of bouillon, with two crackers, are substituted for the milk.

17th to 24th day. 7 a. m., two soft eggs, 10 grams of butter, 50 grams of toast, and 300 cubic centimeters of milk. 10 a. m., 300 cubic centimeters of milk, with 50 grams of cracker and 20 grams of butter. 1 p. m., 50 grams of broiled lamb chops, 50 grams of mashed potato, 50 grams of toast, 10 grams of butter, and 200 cubic centimeters of bouillon. 4 p. m., same as at 10 a. m. 6.30 p. m., 300 cubic centimeters of milk and farina, 50 grams of cracker, and 20 grams of butter. 9 p. m., 300 cubic centimeters of milk.

Since 1903, the author has added raw eggs to this diet, beginning with two on the first day and increasing one a day until eight a day are taken. After two weeks, soft eggs may be substituted.



MIDDLESEX HOSPITAL REGIMEN (STARVATION DIET).

This diet is intended for cases with pain, vomiting, and hemorrhage, especially the latter.

- 1. Starvation until epigastric tenderness disappears, usually the 3d to 10th day. During the starvation period, give water per rectum, beginning with five ounces, increasing to eight and finally to 10. When the patient can tolerate 10, give this amount every four hours. Wash out the colon every morning with one to two pints of water.
- 2. Graduated feeding, beginning with equal parts of milk and lime-water, one ounce of each every two to four hours, gradually increasing dose and time interval. The milk may be thickened by Plasmon or Glidine.
- 3. Next, junket, custard, jellies, and meat extracts are allowed. Still later, calves' and sheep's brains. When these are well tolerated, tripe, sweetbreads, stewed sheep's tongue, flat-fish, and milk puddings are allowed. As the food is increased, the enemata are gradually discontinued.

The accessory medication consists of calcium lactate, 15 grains in 10 ounces of water every four hours per rectum, for hemorrhage; chloretone, 10 grains in 10 ounces of water per rectum, every four hours for restlessness and vomiting; oxygen inhalations a few minutes at a time for vomiting; and 10 minims of 3½ per cent solution of peroxide of hydrogen twice daily, in a capsule prepared at the bedside.

THE LENHARTZ REGIMEN.

- 1. Absolute rest in bed for at least three weeks—longer in severe cases.
- 2. Avoidance of all mental excitement.
- 3. An ice bag to the epigastrium for the first two weeks of the cure.
- 4. Bismuth subnitrate 30 grams, two to three times a day.
- 5. The following diet:

Day.	1.	2.	3.	4.	5.	6.	7.	8.	9.	10.	11.	12.	13.	14.
Eggs.....	2	3	4	5	6	7	8	8	8	8	8	8	8	8
Sugar with eggs (gm.)..	0	0	20	20	30	30	40	40	50	50	50	50	50	50
Milk, cc.....	200	300	400	500	600	700	800	1000	1000	1000	1000	1000	1000	1000
Raw chopped meat (gm.)	0	0	0	0	0	35	70	70	70	70	70	70	70	70
Milk rice (gm.).....	0	0	0	0	0	0	100	100	200	200	300	300	300	300
Zwiebach (pieces) .....	0	0	0	0	0	0	0	(1)	2	2	3	3	4	5
Raw ham (gm.) .....	0	0	0	0	0	0	0	0	0	50	50	50	50	50
Butter (gm.) .....	0	0	0	0	0	0	0	0	0	20	40	40	40	40
Calories .....	280	420	637	777	956	1135	1588	1721	2138	2478	2941	2941	3007	3073

1 20 gm.=1 p.

The milk and eggs are given separately, according to the original diet, but may be mixed. A small amount of good sherry may be added. The milk and eggs are prepared in a covered glass tumbler surrounded with cracked ice, and kept at the bedside. The feeding spoon is kept iced in the same manner. The patient is fed by spoonfuls by the attendant.

Up to the 10th day, food is given at hourly intervals from 7 a. m. to 9 p. m., the egg and milk mixture being divided into 15 equal portions. There is complete rest during the night.

From the 11th to 14th day, the interval of feeding is made two hours, and the milk and egg in 6-ounce doses with ½-ounce of raw egg.

From the 7th day on, one-half of the eggs may be given in the form of soft-boiled eggs.

The solid food, rice, scraped beef, ham, and soft-boiled eggs, are best given at periods which would correspond during health to regular meal hours.

As suggested by Lambert, finely chopped cooked chicken can be substituted for the raw meat and ham in the original diet.

The following table from Lambert gives the dietary in different form:

Day.	Eggs.	Milk.	Sugar.	Scraped Beef.
I.	2 dr. per dose; total, 2 eggs.	4 dr. per dose; total, 6 oz.		
II.	3 dr. per dose; total, 3 eggs.	6 dr. per dose; total, 10 oz.		
III.	½ oz. per dose; total, 4 eggs.	1 oz. per dose; total, 13 oz.	(1)	
IV.	5 dr. per dose; total, 5 eggs.	1½ oz. per dose; total, 1 pt.	(1)	
V.	6 dr. per dose; total, 6 eggs.	14 dr. per dose; total, 19 oz.	30 gm.	
VI.	7 dr. per dose; total, 7 eggs.	2 oz. per dose; total, 22 oz.	40 gm.	36 gm. in 3 doses.
VII.	4 dr. per dose; total, 4 eggs. Also, 1 soft-boiled egg every 4 hrs.; total, 4 eggs.	2 oz. per dose; total, 25 oz.	40 gm.	70 gm. with boiled rice, 100 gm. in 3 doses.
VIII.	.....do .....	2½ oz. per dose; total, 28 oz.	40 gm.	Do.
IX.	.....do .....	3 oz. per dose; total, 1 qt.	40 gm.	Beef same. Rice, 200 gm. Zwiebach, 40 gm. in 2 portions.
X.	.....do .....	Add cooked chopped chicken, 50 gm., also butter, 20 gm.	40 gm.	Do.
XI-XIV.	Interval of feeding made 2 hrs., milk given in 6-oz. doses, with ½ oz. of raw egg. Butter increased to 40 gm., and various additions made, as detailed above.			

1 20 gm. added to eggs.

In cases with hemorrhage, no attempt should be made to move the bowels for the first week; after this, enemata may be used. In cases not complicated by hemorrhage, enemata are also the best means of moving the bowels.

HORT'S REGIMEN.

- 1. Care of the mouth and teeth, with especial attention to pyorrhœa and caries.
- 2. Purgative pill every night for two weeks.
- 3. Restriction of the fluid intake. Tea, coffee, and alcohol absolutely forbidden. Soups, broths, beef-tea, and milk usually excluded.
- 4. Rest. 10 to 14 days in bed, and 10 to 14 days in a reclining chair.
- 5. A dry protein diet, mainly meat at frequent intervals. For example:

Breakfast, toast with butter and lightly cooked eggs.  
11 a. m., two to three ounces of raw beef juice, freshly made.  
1 p. m., beef, mutton, or lamb, served as joint, steak, chops, or cutlet, lightly cooked and served in fresh gravy, without vegetables. This is the entire meal, except toast or one or two rusks, with butter if preferred. The amount of meat is regulated by the appetite.  
4 p. m., same as breakfast.  
7 p. m., same as 1 p. m.  
9 p. m., same as 11 a. m.

If there is pain in the night, small sandwiches of stale bread and pounded chicken are allowed. This diet is gradually worked up to during the first week. Once established, it should be continued for a month after the patient goes back to work.

- 6. Ten cubic centimeters of atoxic, sterile horse serum or sheep serum, three or four times a day, immediately after food, in half an ounce of cold water.

In bleeding cases:

- 1. Ice water through an oiled stomach tube.
- 2. Morphine and atropine.
- 3. Subcutaneous injections of horse serum.
- 4. No food for one to two days.
- 5. For three days, jellies, soft eggs and pounded chicken until all the hemorrhage ceases.
- 6. After this, the preceding diet.

JAROTSKY'S EGG AND OIL DIET.

The egg and oil are given separately, the egg in the morning, the oil in the afternoon, with several hours interval between them. At the beginning of the treatment, patients receive the white of



one egg in the morning, and 20 grams of olive oil in the afternoon. Each day the white of one egg and 20 grams of olive oil are added to the amount given the day previously. The eggs may often be increased to eight a day, and the oil to 120 to 140 grams daily, or more, if the patient can tolerate it. In patients with bleeding ulcers, no food is given by mouth for two or three days, and during this period the patient receives nutrient enemata, or the egg and oil diet is restricted to one egg and 20 grams of oil daily, until the hemorrhage ceases. The nutrient enemata are given until the diet is increased to a point where the patient is taking the whites of several eggs a day; they are then gradually discontinued.

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## STUDIES IN PNEUMONIA.

## ABSTRACT OF PAPER.

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It is of importance to obtain, if possible, further knowledge concerning the nature of the intoxication in pneumonia, for two reasons; first, to furnish a more definite conception of the pathological process in this disease, and, second, because the discovery of a specific toxic substance might possibly lead to the discovery of means of neutralizing it, and thus to improvements in the therapeutic measures employed.

It has so far been impossible to detect by chemical or biological means the presence of poisons, either in the media in which pneumococci have been cultivated or in the body fluids of animals dying from infection with these organisms. Lately considerable stress has been laid on the importance of bacterial anaphylatoxins, as described by Friedberger, in producing the symptoms of infection. The anaphylatoxin theory assumes that the intoxication is due to split products of the bacterial protein. According to Friedberger the ferment causing the splitting is supposed to be present in the serum, but the demonstration by Neufeld and Dold, and also by Rosenow, that autolyzed bacteria, in the absence of serum, are toxic has required that the theory be modified so as to presuppose that the ferments are present in the bacterial bodies. We have been able, however, to show that the bacteria simply dissolved in dilute solution of bile, or even brought into solution by freezing and grinding, are also toxic. Since in the latter ex-

periment digestive processes can, with all probability, be excluded, it seems reasonable to believe that the toxic effects produced by these various solutions are due to preformed substances within the bacterial cells, which are set free when the bacteria go into solution. We have also shown that such solutions of bacterial cells are hemolytic. By immunization of animals it has been possible to produce a serum which neutralizes the hemolytic effects of the toxin, but, so far, it has been impossible to obtain a serum which neutralizes the toxic effects.

The evidence is still very inconclusive, however, that either one of these reactions is of significance so far as intoxication in lobar pneumonia is concerned. The experimental evidence indicates that the symptoms are due to the action of the living bacteria, rather than to the action of substances contained within the dead bacterial cells. Pneumococci, when growing in blood-containing medium or when growing within the animal body, are able to transform oxyhemoglobin into methemoglobin. An analytic study of this reaction has suggested a possible way in which pneumococci may produce their effects, without the production of a soluble poison. This study indicates that the transformation of oxyhemoglobin into methemoglobin is due to a modification of oxidation and reduction processes in the medium immediately surrounding the bacteria.



If this be true, it is possible that an analogous reaction may be responsible for the toxic action of pneumococci on tissue cells. A difficulty, however, arises in applying this theory to pneumonia, since early in the disease there is apparently no wide distribution of the organisms. It is conceivable that in the early stages the symptoms are non-specific in character, and only in the later stages of the disease, when the pneu-

mococci are widespread throughout the body, is the intoxication truly specific in nature.

It is not believed that the studies so far carried out give any definite indication of the essential nature of the intoxication in pneumonia. The observed facts suggest certain conceptions, but only further work can show whether or not they are of significance.

## THE NERVOUS PATIENT.

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Leaving Baltimore some seven years ago, after 13 years of very happy work, I served for three years as superintendent of a medical institution designed for the care of fatigued and nervous as well as organically ill patients. Here I saw, by scores and even by hundreds, illustrations of the various types of nervous disorders including the rarest. Of course, I could not study very many of these cases carefully, I had too little time for that, but such observation as I was able to make may be worthy of your attention. Dr. Henry M. Hurd, commenting on this opportunity, assured me that there I could reap a rich harvest of clinical experience, and such proved to be the case. It had been my good fortune here to be associated with Dr. Lewellys F. Barker as his assistant and I left The Johns Hopkins Hospital inspired and encouraged by his splendid work in the diagnosis and treatment of nervous patients, patients who suffer perhaps more severely and who are more neglected than any other group found in hospital wards. It is with pleasure that I now acknowledge my debt of gratitude to Dr. Barker for the inspiration which my association with him gave me.

A study of the so-called functional nervous disorders is indeed timely. In the evolution of modern medicine this now is the problem at hand. Physicians 25 years ago spent the most of their time worrying over the differential diagnosis between the various acute infectious diseases, especially typhoid fever, diphtheria, syphilis, malaria, etc., but now this is in large measure the problem of a laboratory assistant, and the treatment of such patients is much a matter of ward routine. The hours thus saved can now be spent studying and treating patients formerly neglected. So closely related, however, are the functional neuroses to the infectious diseases, that until the diagnosis of the latter could be, in some degree at least, quick and accurate, the study of the former remained unprofitable. The group of functional nervous diseases is a subject in which the general practitioner should receive careful training, for neurasthenic patients haunt the office of the family doctor and it is he who often must decide early, if treatment is to be given while the condition is curable, whether the "neurasthenia" of the patient before him means a psychoneurosis, a latent serious physical disease, disappointed love, a guilty conscience, or early insanity; and the fate of the patient sometimes hangs on this early and often very difficult diagnosis.

The neurasthenic group is protean in character. Like the class "Vermes" of Linnaeus, which included the whole of the animal kingdom remaining after the easily defined classes had been separated, so "neurasthenia" is the "waste-basket" of the general practitioner. The neurasthenics form a group of patients not separated but left; it is a group of patients with conditions which may resemble each other superficially, but which usually have no possible relationship the one to the others and which may need in each case very different treatment. That is, the diagnosis neurasthenia is a confession of failure in diagnosis. Neurologists now try to use this term in a technical manner, but they do not agree among themselves and their discussions usually only mystify still further the general practitioner.

During the past few years I have tried, but in vain, to be obedient to the vision of modern Freudian psychology and psychotherapy. Unfortunately I have not worshipped at the shrines of Vienna and Zurich, and so the Freudians may claim that I, not properly initiated, should have no opinions to express. Since much that I shall say will be in criticism of this doctrine, and will therefore not be "in popular style" to-day, I desire to present my views before this audience first, preferring punishment at the hand of my Alma Mater, since it will be helpful, although painful, to that of my more hostile foster father, the professional world. The conclusions which I shall present here are not all new, in fact some of them were stated by others years ago. Nor shall I attempt to discuss many points, for to establish one in this difficult field would be an achievement. He who attempts to classify and explain the full group of the psychoneuroses is indeed bold; he is also ignorant, for surely very little of this dense clinical jungle has as yet been cleared.

Among the symptoms of the neuroses are two groups of phenomena; the disease-phenomena and the defense-phenomena. In teaching medical students the treatment of pneumonia, for instance, one emphasizes the importance of the defense-phenomena, in order that the students may not injure the patient by symptomatic treatment. Our habit of speaking of diseases as entities is unfortunate. There is no such *thing* as a disease, but there are diseased men and women. We personify typhoid fever, for instance, since all persons infected by *B. typhosus* are apt to react to this infection in much the same manner. The bacterial toxins are injurious



to the body and the body defends itself. The symptoms of the infection are for the most part manifestations of this defense. The student at first desires to "bring down" the fever of the patient ill with pneumonia, and yet the rise of temperature is a part of the defense against infection. He wants to lessen the cough, and yet cough is a protective act to get rid of some of the sputum; then he would try to diminish the amount of sputum, but this is an exudate designed to neutralize a toxin. The leucocytosis is a part of the fight. The laboratory diagnosis of an infection is the isolation of the infecting organism itself, or the demonstration of a specific protective substance (*e. g.*, the agglutination test for typhoid infections). In fact, our proof that a given organism is pathogenic is the demonstration that the body actually defends itself against it. High blood-pressure certainly is protective in nature, so are most pains; and the same can be said of very many so-called symptoms of disease.

Among the symptoms of the nervous diseases are protective phenomena of considerable importance, which, like the amino-acid nuclei of various proteid molecules, can be "split off" from the syndromes of unrelated conditions. It is important to distinguish these from the injurious factors also present. One of the most obvious of these protective "nuclei" is the asthenia which forms so conspicuous a part of many nervous conditions. The fatigue produced by overwork is a fairly simple condition and will serve us as a good starting-point in this discussion. One of the first evidences of the mental fatigue of a professional man is the warning sensation of physical and mental tiredness. The second is contraction of the field of mental vision, due to a great reduction in the efficiency of operation of the mechanism of memory by association. "The field of view of consciousness," says James, "varies very much in extent, depending largely on the degree of mental freshness or fatigue. When fresh our minds carry an immense horizon with them. But under ordinary conditions the halo of felt relation is much more circumscribed." The successful research worker must be a man with wide horizon; when tired he becomes a routinist, and does not see the various ways of approaching and successfully solving his problem, but plods on faithfully and laboriously, blind to the avenues to success which would open to him were he rested. A well-known scientist who is very productive in his researches works only from nine o'clock in the morning to one o'clock at noon each day, and yet accomplishes more than do his more studious co-workers who plod all day. The school-teacher fresh from her vacation sees the multitude of various ways that she can present the daily lesson to the individual boys and girls, but when tired her ingenuity ceases and she teaches "classes." The clergyman when fatigued will with great earnestness preach commonplace, routine sermons and cannot understand why some pews are empty. The fatigued doctor treats his patients faithfully but not skilfully, for he does not see and so fails to treat the little individual differences that every case presents. The fatigued surgeon performs his routine operations in a routine way and does not see the opportunities to individualize each case, thus improving the

result for each patient. The great men of science have been intense but not "chronic" workers. In fact, the efficiency of a mind searching for truth seems to vary in almost indirect algebraic proportion to its fatigue. We would suggest, judging by a few experiences, that much of the frequently discussed "mental activity during sleep"—for instance, the successful solution in the morning of problems unsuccessfully attempted the evening before—is really evidence of the remarkable efficiency of the mind fresh after sleep, able in the early morning in a few moments to accomplish what hours of work the evening before could not. This limitation of the field of vision is an actual mental reduction, temporary and physiological it is true, but, nevertheless, while it lasts a mental reduction as truly as that of the patient with dementia. It is also a protective phenomenon, and should be so considered in diagnosis and in treatment, for it is the substitution of an easy method of work for one much more fatiguing.

Another symptom of mental fatigue is distaste for customary work. This is akin to negativism and is protective in nature. The school-teacher goes reluctantly to school; the clergyman must control his temper when urging himself to his work; the doctor hates to hear the telephone bell ring. And yet each on returning from his vacation attacks his work with zest. These symptoms are protective, discouraging and inhibiting further effort, and analogous to the fatigue of the neuromuscular apparatus which inhibits work while still there is a wide margin of safety.

These fatigue symptoms may reach extreme degrees, provided certain emotional elements are not aroused. One case may perhaps illustrate a group: a man who showed such marked mental reduction without retardation that he was sent to us with a provisional diagnosis of dementia. We were asked to give him a brief trial and commit him to an asylum if necessary. Yet in three weeks he was well and he stayed so. For 22 years he had not taken a vacation of over 24 hours' duration. But his work was of a purely routine nature, and he did it well; his employers were evidently content and so was he. No emotional elements supervened in his case.

We do not refer to patients of this group as neurasthenic, but call them "fatigued cases." One reason why this fatigue symptom complex should be emphasized is that the success of treatment of patients with simple fatigue has misled neurologists. These cases appear at first much more serious than they really are and so some elaborate course of psychotherapy is at once begun. The patients promptly recover (as they would with rest and partial isolation alone), the treatment is given the credit for the result and is at once practiced on other forms of functional neuroses.

Emotional factors, however, usually enter soon, and change radically the symptom complex. That wide margin of safety between fatigue-inhibition and injury is invaded; the patient becomes "neurasthenic." The point at which these various emotional factors enter depends much on the individual—his pride, his feeling of responsibility, or his financial needs. He worries because the quality of his work is not up to his standard, and this hurts his pride. It is of interest that



he considers the quality of his work much worse than it really is. He fears that he may lose his employment and be unable to support his family. He becomes self-accusing, he belittles himself, he weeps; he becomes suspicious, feels that others are watching him, that every laugh he hears is at his expense; his feeling of inadequacy increases, and the increasing sense of incompleteness adds to his misery, for now he fears that he is losing his mind. Thus is his fatigue greatly increased, and so also, as a result, are the reasons for his worry. And although the quality of his work actually does suffer and the reasons for his worry become more real, yet his self-criticism and his fears grow in intensity far more rapidly than facts justify. This must belong to the group of defense-phenomena.

Emotional processes are of themselves intensely fatiguing, "more so," says Dejerine, "than the most violent exercise or most intense intellectual work." The emotion leads to greater fatigue, the greater fatigue to much more emotion. Insomnia usually results, which naturally increases the fatigue; the appetite for food is modified and the digestion is affected, this leading to gastro-intestinal disturbance, and all these to greater fatigue and this to stronger emotion. Thus whirls the vicious circle.

This is the group which crowds our sanatoria. These patients certainly are neurasthenic, but are they cases of neurasthenia? This of course depends on one's definition. Dejerine says, "No." "Wipe the simple elements of fatigue and exhaustion out of the neurasthenic picture." Our diagnosis, in order to avoid confusion is, "neurasthenia due to mental fatigue." As treatment, a few weeks of separation from work in a quiet environment usually leads to a very satisfactory recovery, for the emotions often decrease in intensity with, or even faster than, the fatigue. No elaborate psychanalysis or psychotherapy is necessary.

This diagnosis, "neurasthenia due to mental fatigue," for reasons which will appear later, we reserve for those cases only which comply with the following conditions: The patient must have a history of a normal childhood and adolescence, and of previous efficiency in his chosen line of work. These points in the history should not, as a rule, be obtained from the patient himself, for he is a poor judge of his own boyhood and later success, but from wife, parents, or friends.

This fatigue nucleus is that which brings many psychasthenic patients to us for treatment. They bear with their obsessions and phobias until tired out and worried—that is, until they become neurasthenic. After a rest cure they sometimes return to work encouraged, although their mental stigmata are unaffected. For the diagnosis psychasthenia, the history of abnormal childhood is very important; they lack the play-spirit; are too conscientious; are over-sensitive; are over-religious; develop early phobias, etc. These patients when we see them are, we consider, definitely and permanently mentally defective. We therefore give them advice similar to that we would give an adult with kyphosis. We would not encourage him "to try to always stand up straight," for this would be not only useless but would add to his unhappiness.

We encourage him to accept his condition and try to make the best out of life he can in spite of it. The real problem in psychasthenia is to prevent its development by better care of infants by parents.

In the insane conditions also the fatigue nucleus is sometimes important, but usually it is overlooked. The maniacal patient surely fatigues himself more rapidly than does the normal worker; insane delusions arouse emotions perhaps more intense than are those of the neurasthenic; surely the effects of these factors in the insane must be similar in character to those in normal persons. It has seemed to me, although I defer to those better able to decide this point than am I, that one secret of the success of the modern treatment of the insane with its comparative freedom, fresh air, good food, and occupational therapy, is that the emotions are less aroused than they would be by barred windows, the maddened and maddening environment, and the tedious and enforced idleness of the asylum. At any rate it is probably true that such treatment results in milder and shorter cases.

In cases belonging to the group which we desire to discuss next, the emotional element is the primary cause of the fatigue. Too sharp distinctions cannot, however, be drawn between these groups, for patients in the former group tend naturally to end in this if sufficient time be allowed. A secret grief, an unfortunate love affair, the fear of some serious organic disease, the pangs of conscience, the fear of disgrace, all can lead to extreme fatigue. It has impressed me, however, that closed incidents have very little value as exciters of emotions. A love affair really ended, a misdeed from which one has no longer any grounds for fear, are little dangerous. It is the fear of a future punishment, either in this world or in the next, or the cherished hope of a future reversal of fortune which injure. This is the ground for our advice "Forget it," or "Cast thy burden on the Lord," or "Enlist in activities which are antagonistic to the former," etc. It is the emotion to which one clings which consumes him. We say this since it is hard to believe that "psychical traumata" received in childhood, long since forgotten, and which are now without fear of consequences for the future which would appeal as reasonable to a practically normal man, can do much harm. And yet we may believe they do. The buried complex doubtless is important in some cases. An emotional reaction of a certain character to definite classes of experiences may become a habit, but this is subject matter for others. My plea is for the ninety-nine patients; not for the one.

But the above three sentences are a parenthetical digression. We must return to our description of cases we have seen. The vicious circle starting with the emotion produces fatigue, then is added more emotion due to the consequences of this fatigue, then digestive trouble and insomnia, and we soon have a condition similar to that which begins with fatigue, but more serious, for simple rest and recreation alone will help little so long as the emotional element still has reason for its continuation. In cases of the former group many of the emotions were grotesquely exaggerated and the first result of isolation and rest is that these lose their inflated values; but



in these cases the original emotions have more genuine value. In order to avoid confusion we classify these cases as "neurasthenic due to concealed worries." These are the cases which the confessional, as well as psychoanalysis helps. Granting that my lack of training in the field of psychoanalysis has allowed many difficult cases to slip through my fingers, yet I am convinced that these patients, women especially, understand their worries altogether too well, although they may try to conceal them from the world. Indeed, they may succeed in deceiving themselves, but in my experience these periods of forgetfulness are periods of improvement. I have been impressed with the number of patients who do their best to deceive themselves and the doctor concerning some important concealed worry, and who, after two or three consultations, return and say, "There is something I forgot to tell you," which, being translated, means, "I have decided you are the proper person in whom I can confide." In this connection it is interesting to note how many of the cases reported by Stekel<sup>1</sup>—and I judge that Stekel represents worthily the Freudian school—were only too well aware of the concealed emotions or sinful habits in their lives, although they were indeed surprised that Stekel should have explained their symptoms as due to these. Finally, one is not at all convinced that the perfect relief of symptoms after such explanation is any proof that these symptoms and the habit had any previous connection.

Worries enter the lives of all normal men and women. It is the concealed, cherished, fostered worries or griefs which in time become disastrous.

In this connection mention should now be made, by way of contrast, of the memories which follow the single unusual shocks, as railroad accidents, earthquakes, mine accidents, etc. which come into the life of a few men. The occasional mental results in between 20 and 25 per cent of those who meet with these experiences and who themselves received no physical injury are termed "post-traumatic neuroses." There is, perhaps, no more difficult group to understand, especially in those cases uncomplicated by legal problems, yet it would seem as though they belonged in a quite different category from fatigued neurasthenic conditions, although Sterlin<sup>2</sup> considers them in the same class. He found that the patient is as truly abnormal during the period immediately following an accident, usually spoken of as the "latent period," as he is during the later more conspicuous period of depression. The first period is marked by insomnia, or broken sleep with terrifying dreams, increased reflexes, high and variable pulse, vasomotor instability, and other evidences of hypertonia.

Another question which often arises in connection with nervous conditions is, can a normal mind be unbalanced or even made neurasthenic by griefs, especially by those which we must consider as more or less inevitable, such as the death of relatives? Any one who makes a practice of observing or obtaining the history of as many normal persons as possible must be surprised at the fearful nervous strains some persons

can undergo with apparently no bad results at all. The death of several members of the family one after another is borne with courage, and their testimony, "I felt as badly as was possible when the first died—I could not feel any worse when the others followed," may give a hint of the existence of a protective mechanism and also justify the often employed figure of speech, "Cup of sorrow full to overflowing." That is, a normal person is capable of suffering safely a certain amount of grief, and this cup full the excess overflows inflicting no injury. Those patients whom grief has injured sometimes give a history of former nervous abnormality, while in a perhaps larger number of cases we find that the reason for the grief aroused also other emotions, such as shame, disgrace, or self-reproach, and these are what injure.

How important the shocks of childhood are is uncertain. It is certainly remarkable how well they are usually borne. I have been impressed when taking the stories of children concerning the immediate past how inaccurate they are. The law in Indiana states that the testimony of a child may be received, but it is for the court to decide how valuable it is as evidence. In other words, the child is an unreliable witness concerning the immediate past. How valuable then can be the memories of childhood, of events of 30 or 40 years before and forgotten for years? Of course, patients are very apt, during depressed periods, to ascribe their present mental suffering to some event of the long-forgotten past, but we ascribe this to the hunger of the disturbed mind for a cause for its suffering, and we know how easy it is for us to furnish them with a cause from their past history, and especially one connected with sexual irregularities.

But the largest neurasthenic group of all consists of patients whose primary fatigue is due to latent physical diseases. By "latent diseases" we mean those which for a while at least give no characteristic or localizing symptoms. In the old definitions of neurasthenia, "somatic symptoms of psychical origin" were emphasized as necessary features. But the purely psychical origin of all of these aches and pains may be questioned. Symptoms (by which we mean subjective sensations as distinguished from objective "signs") are very often due, not to the disease itself but to some of its minor or secondary features. There are practically no symptoms of gall-stones as long as they remain quietly in the gall-bladder; a cancer of the stomach on the lesser curvature and not interfering with either orifice causes no localizing subjective symptoms, but a cancer of similar nature and size an inch nearer the pylorus may cause the greatest distress. Of serious organic diseases the only symptom (subjective) felt at first and even for a long time in many cases is easy fatigability, and since unfortunately few general practitioners look carefully for objective signs of disease if the patient's story does not suggest one, these patients are treated for neurasthenia during that period when their incipient trouble would be most amenable to treatment and until more definite symptoms appear. The cause of this fatigue in chronic infection is, without much doubt, the toxic bacterial proteids of the infecting organism; in other cases, possibly the toxic products of an abnormal

<sup>1</sup> *Nervöse Angstzustände und ihre Behandlung.*

<sup>2</sup> *Deut. med. Wch., Nov. 2, 1911.*



catabolism; in still other cases, as in chronic myocarditis, the inefficiency of a weakened organ. This easy fatigability cannot fail to awaken the patient's apprehension if it disturbs his activities, and in proportion as the emotional element is aroused will the patient become neurasthenic.

Of the latent infections most important in the production of neurasthenic conditions are, chronic tonsillitis (often without sore throat), chronic nasal sinusitis, chronic appendicitis, pelvic inflammatory disease, and various mild ambulatory fevers, as typhoid and malaria. It is very interesting that tuberculosis is not always a neurasthenia-producing condition. Some patients are stimulated to unusual efforts during the febrile period of this disease. In this group we place also that unfortunately very large number of drug habitués, since the general mechanism for the production of their neurasthenic conditions would seem to be similar.

Malignant disease during the so-called latent stage, chronic Bright's disease, organic nervous diseases, especially locomotor ataxia and general paresis during their early stages, slight chronic myocarditis, arteriosclerosis, all explain many cases of so-called neurasthenia. Sanatorium physicians must correct the diagnosis in at least half of the cases sent them for rest treatment. By no means do all or even many of the patients with these conditions become neurasthenic, and this is particularly true of persons beyond middle life. It is astonishing how advanced and serious may be the still latent organic disease of some elderly patients. They do not realize that they are at all ill, provided they do not discover that their sphere of activity is progressively narrowing. Automatically and unconsciously, so far as these patients are concerned, the insidiously increasing easy fatigability removes or inhibits the desire for effort; the patients do less and less as the disease progresses, and yet often will assert with considerable feeling that they feel as well and are as active as ever. The hope for the future, so far as the conquest of the so-called incurable diseases of middle life is concerned, is a medical profession trained to examine carefully every patient, and who will treat him for his real condition, not for neurasthenia. It is indeed the rapid advance in laboratory methods of diagnosis, in Roentgenology and in exploratory surgery which is revolutionizing our ideas of the functional neuroses. It is unfortunate that some of these physicians who are especially interested in the psychoneuroses pay so little attention to the methods of accurate physical and laboratory diagnosis, but spend their time studying the disturbance of the mental mechanism which the patients present. Only in this way can we explain the radical views published from certain clinics. It is, of course, true that mental symptoms must depend on a disturbed mental mechanism, but to study this mechanism as entirely distinct from that of the physical organs is to turn the wheels of progress back to Spinoza.

Disorders of the ductless glands we now know explain some of the so-called neurasthenic conditions, and we may well believe that as knowledge of their functions and disturbances grows they will explain still more of that large number whose origin is still so uncertain. Concerning the importance

of the thyroid gland, at least, we have accurate information. Mild cases of hyperthyroidism without goiter, without exophthalmus, and with pulse not constantly rapid, are common and are easily misinterpreted. These patients are nervous in the sense that they are high-strung, restless, easily irritated, attempt much but accomplish little, have a feeling of "internal tension," and perspire easily but not profusely. A positive Graefe sign can often be elicited, and fine tremor. If to these patients be given a little thyroid extract (five grains three times a day for three days) all these symptoms become much exaggerated.

There is also a fairly large group of patients suffering from mild hypothyroidism yet without myxedema. They complain of physical and mental languor, of a sense of increased inertia, of difficulty in starting to do anything, which they explain as laziness, of inefficiency, of a feeling of worthlessness, and of a sense of the progressive limitation of the sphere of their activities. These feel very much better after a few doses of thyroid extract. The cases of pituitary trouble have aroused considerable interest, and in a few cases of "neurasthenia" we have seen much improvement follow the administration of pituitary extract. We believe, in fact we know, judging from the phenomena of adolescence and of the menopause, that disturbances of the sexual glands are important in the production of neurasthenic conditions; in fact, few beliefs are older and more firmly rooted than this, but unfortunately our evidence on this point is not as yet accurate and convincing. Some modern neurologists maintain, however, that patients suffering from the disturbed functions of physical organs are not true neurasthenics; that neurasthenia is due to disturbances of the mental mechanism, produced in large measure by emotions. But can this mental mechanism be thus radically separated from physical disorders, except by a purely mental process? Neurasthenia may be defined (as can all mental phenomena) as a disturbance of the stream of consciousness; a stream that flows on rapidly in the case of hyperthyroidism; sluggishly in myxedema; with whirlpools, cataracts and rapids in the patient with mania, or scarcely at all in melancholia. But, granting that a stream in its flowing obeys the laws of water, its course is determined by the shape and pitch of its river-bed of earth and rocks. So the "shape of the bed" for the stream of consciousness is determined to no little degree by the internal secretions.

Psychasthenia is, as mentioned above, a very different condition from those discussed in this paper. There we have a mental defect, congenital or acquired early in life. Hysteria, with its definite stigmata, is still another problem. But there is still another and a large group so often considered a "simple neurosis" that we should include it in this paper. I refer to the patients with very mild depression, often so slight that they can control it well, who live an apparently normal life, their mental suffering unsuspected by their friends. All have been impressed by the regularity of the recurrence of these attacks of depression, each seven to ten years. This condition is not at all easy of recognition if the patients care to conceal their symptoms. They seem unhappy, inefficient



and "nervous." But the importance of a correct diagnosis is only too well emphasized by the consideration that while the average patient with the conditions which theirs simulate will be well in a few weeks, they may consider themselves fortunate if well in 12 months.

In addition to these cases of mild manic-depressive psychosis, we have the depression of the menopause in women, and that very similar condition in men of the sixth decade. These cases when mild may be considered as simple neuroses. I wish to emphasize again that feelings of depression of similar quality may be induced, and an insane depression intensified by eye-strain, nasal obstruction, and various gastro-intestinal conditions, with fatigue.

We now desire to discuss some of the symptoms common to many psychoneuroses, their possible origin and their significance.

One of the most important causes of nervous fatigue and source of many of the neurasthenic symptoms is eye-strain.\* This is not surprising, considering the importance of vision and of visual memories in our mental life. The most common of these symptoms is headache. Few headaches are the immediate result of eye-strain. Indeed, very few headaches are due to any one cause. Usually the chain of their causation has two or more links, and many patients whose error of refraction would suggest headaches have never so suffered. Most headaches resemble the result of bringing into proximity a lighted match and a keg of gunpowder—neither of them alone sufficient for an explosion, but together they are quite adequate. We may speak of headaches as systematized conditions, as conditions requiring the development of an effective mechanism, but the notable truth is that they are reactions of the patients to certain conditions. Eye-strain is but one factor, and yet when this is relieved these headaches stop, whether they "through habit" are accustomed to occur only in the morning, or only at evening, or always at the end of the week, or only during nervous strain, or, in the case of women, only during menstruation. Eye-strain is in large measure the result of asymmetrical astigmatism, that is to say, of irregularities in the shape of the eye-ball and the resulting abnormalities of function of the ciliary muscles. We recognize that certain families have noses, chins, etc., of certain shapes, which we refer to as family types. This is true of the eye-ball as well. But while the shape of the nose or chin has relatively little influence over its efficiency, it is far different in the case of the eye-ball. We speak of headaches as inherited, and surely there would seem to be few troubles as certainly inherited in certain families as are headaches; but it was not the "ache" which was handed down from generation to generation, but asymmetry in the shape of the eye-ball, an anatomical characteristic.

We would not claim that all or that nearly all headaches are due in part even to eye-strain. The headaches which we believe are due to eye-strain have certain characteristics. One of the most important of these are the definite changes in the character of the attacks at certain periods of life. In

most cases the headaches are paroxysmal sick headaches in young adult life, and later, as presbyopia develops, they become more neuralgic in character, less paroxysmal, less acute, more prolonged, while the gastric features become less pronounced and finally disappear. In some cases the headaches cease altogether as the ciliary muscles weaken (this explains one argument in favor of the inherited character of the headache, since in several generations the attacks in each case have stopped at almost the same age); in still other cases, formerly free from pain, the "neuralgias" start with the onset of presbyopia. Of course, eye-strain headaches differ much in location and in character, nearly always, however, is the pain superficial.

The various "equivalents" of headaches are very important. These symptoms seem to have the same significance as the headaches and yield to the same treatment. Again, I would insist that the almost identical symptoms in different persons are not of necessity due in all to the same causes. Headaches and their equivalents are not immediate consequences of eye-strain, but rather are reactions on the part of the patient to these causes. Some have a "check-rein" feeling in the neck, some the sense of a tight cap on the head, or the sensation of the hair standing on end. Most important of these equivalents are the interesting "painless headaches" of childhood, a history of which can be obtained only by careful questioning. We refer to the prolonged spells of crying, for which the child gives no satisfactory explanation, which occur especially in the afternoon after school. Other children at such times are cross and unhappy, others wish to be alone and will even lock themselves in a dark room. These attacks later, at about puberty, are substituted for by sick headaches, and these in the fifth decade or thereabouts in their turn by "neuralgia."

Another equivalent was well illustrated in the case of a very intelligent patient with severe asymmetrical astigmatism, who has never had a real headache or other uncomfortable symptom about the head except during sleep in dreams. When she dreams that her head is aching and that persons about her are suffering in this way, she knows that she needs a new pair of glasses, and this attended to, these dreams stop. Mental depression with feelings, judged by the description given by patients, very similar to those of a mild, true manic-depressive psychosis, is sometimes due to developing presbyopia and in these cases is relieved by proper glasses. I cannot but believe that this explains some cases of the mild depression ascribed to the menopause.

That eye-strain may cause reflex gastric symptoms was well illustrated by a proof-reader whom we saw two years ago. She vomited every day, even after nearly every meal, and became so emaciated—she lost about 60 pounds in four months—that malignant disease of the stomach was strongly suspected. This patient had had no headaches and no feeling of tension or discomfort about eyes, face, head or neck. To eliminate eye-strain atropia was dropped into the conjunctival sacs, and the vomiting at once stopped. Glasses were prescribed. Later the vomiting returned when her glasses needed to be changed. In her case the hypertrophy of the ciliary

\* Dr. George M. Gould refracted many of these patients for us.



muscle, as shown by the difficulty of producing complete cycloplegia, was an interesting feature.

Certain phobias are in some cases quite certainly due indirectly to eye-strain, and are protective in nature, the nervous system registering in this way its unwillingness to trust the data furnished it by faulty vision. Some patients remember clearly their fears of childhood, and these are of no small assistance in diagnosis. Among these are the fear of running over a plank over a brook (and some woodsmen never can cross a stream on a single log without crawling on hands and knees), the fear of running on top of a stone wall, of playing tag on the rafters of the frame of a house, and of walking across a railroad bridge on the ties. It requires very little vision to guide one in walking on a smooth sidewalk, but in the above-mentioned situations the feet must be very accurately placed at each step, and the fear aroused is in some cases evidence that the neuromuscular apparatus refuses to depend on the vision. Some men remember clearly that when they were boys they would not walk across the rafters of a house, yet they would willingly climb to the highest point of a tree, in which latter case touch and muscle sense rather than vision guide the movements. The fear of looking down from a high point is in some cases, I am confident, evidence of faulty vision; and in certain cases quite typical agoraphobia, especially when the open space is a busy street, can be corrected by proper glasses. Evidently in these patients the phobia registers an unconscious judgment that this man's vision is inadequate to protect him from accident.

Some patients complain that frequently and for a few moments they have a sense of unreality, the surroundings suddenly becoming dreamlike. This in some cases is corrected by glasses. In other cases a typical depression, the feelings described quite similar to those of mild manic-depressive psychosis, are the result of eye-strain. The experience of one patient impressed me deeply. She had never had headaches nor been subject to depression. The symptoms of presbyopia suggested the need of glasses, but the day after she began to wear her new glasses she became a typical case of mental depression, unhappy, despondent, but without aches or pains of any kind. This lasted several days. Then it was discovered that the oculist had put the left lens before the right eye, and *vice versa*. After this correction her depression at once disappeared.

Brief spells of blackness before the eyes, faint spells not followed by a feeling of physical weakness, may in some cases be evidence of eye-strain. Various feelings of motion may be corrected by proper glasses; for instance, rocking or swinging sensations, especially while at table, and reminding one of the feeling on an ocean steamship which is rocked by high billows; the sensation that the sidewalk is rolling in billows in front of one; the sense of floating upwards, felt especially when one lies down and sometimes so real that these persons cannot refrain from grasping the bed firmly to prevent their floating up to the ceiling. There is one dream which I believe is usually evidence of uncorrected eye-strain, and that is the dream of falling off a high point and, when about to strike

the bottom, awaking with a start that shakes the bed. This may be due, I believe, to relaxation and then spasm of the ciliary muscle as the patient is sinking into progressively deeper sleep, and is therefore somewhat analogous to the night cries of the child with a tuberculous hip.

For all these symptoms Freud probably would have given other explanations, and it may be that in many cases his explanation would be the correct one; but the relief from these symptoms which in some cases follows the proper correction of eye-strain is, we feel, sufficient evidence that in these cases eye-strain is sometimes important in the causation of these symptoms.

The nose and its accessory sinuses are important causes of symptoms described often as of purely psychic origin. No small number of "gastropaths" are really cases of chronic (and painless) infection of the posterior sinuses; some cases of "nervous asthma" need operation; nasal obstruction is more often associated with painful menstruation than is generally recognized; morning headaches of a dull, heavy character and deeply seated and some in the occipital region which disappear during the forenoon are of nasal origin. That exasperating feeling of mental dulness, of inability to talk directly to a person, of a "cloud before the mind," sometimes described as "cobwebs on the brain," often means nasal obstruction. A business man told me he wished he "could take his brain out and wipe off the cobwebs," for he had a feeling as though he were not thinking clearly and quickly or talking effectively with a prospective customer. Six weeks after his nasal obstruction was relieved by operation he wrote that he had accomplished more business than formerly he had done in six months. And, finally, the long-continued psychic depression following la grippe which has led many to suicide, is due, in no few cases, to an infection of the nasal sinuses.

At present, faulty dentition, especially the pressure caused by unerupted molars, is recognized as an important cause of neurasthenic symptoms.

Backaches are often complained of by neurasthenics. The psychanalyst would treat the mental mechanism of these patients and the surgeon would suspend some abdominal or pelvic organ; yet only too often the cause is general muscular asthenia, a faulty position in standing, a slight spondylitis, or in men, chronic prostatitis.

Before we close we may be pardoned if we mention errors based on misinterpretation of the success of treatment. The splendid results of the Weir Mitchell treatment have been responsible in some degree at least for the general belief that neurasthenia is the satisfactory diagnosis of the condition of certain patients. These patients treated for neurasthenia improve remarkably, which seems to justify the belief that this diagnosis must have been correct. But the Weir Mitchell treatment is splendid treatment not only for fatigued patients but for those with early pulmonary tuberculosis, chronic nephritis, many forms of chronic arthritis, for gastric ulcer, while it is followed by temporary improvement in cases with other exhausting diseases. Neither does the improvement following an operation always justify the operation. Without



in any way criticizing the splendid success of modern surgery, I would suggest that some cures may not have been due to the operation as such. In the whole history of medical quackery never has the boldest or most daring charlatan set his stage more adroitly or successfully for intense suggestion or deep impression, as is innocently, unconsciously and unintentionally done daily in the surgical wards of our hospitals. The failure of medical treatment, the hesitating, reluctant suggestion by the physician of consultation with a surgeon, the examination by this specialist, the discussion, the decision, the fear of loss of life, of the anesthetic, then the trip to the surgical ward, the uncanny noises one hears, the gossip of the pupil nurses, the pre-operative treatment, the special clothes for the operating room, the peculiar psychical experiences when going under and when recovering from the anesthetic, the careful nursing, and then the post-operative treatment lasting two or more weeks, with the great attention paid to the diet, the bowels, etc., all make a profound impression on the patient, and it is no wonder that he often leaves the surgery happy

and well, even though the subsequent history shows that the operation was on the wrong organ. In many of these cases it is possible that were the same procedure carried through, but the incision made only through the skin, the result would have been just about as good. In this connection it is interesting that the modern rest cure with its isolation, special nurse, special diet, and carefully planned psychotherapy, does follow much the same lines. But the results of most of the surgical treatment in the case of neurasthenic patients are not at all good. Each operation cannot but be a nervous shock and can be justified only when the probable ultimate gain is quite certain to more than overbalance this primary loss. If a person is clearly neurasthenic the indications for operation should be very clear indeed before one is attempted. Certainly aches and pains no matter how intense, without objective physical signs of definite disease, should not lead to operation. The same pains return, and then begins a series of operations all intensifying the soon almost incurable nervous condition.

## THE DIAGNOSIS OF MEDIASTINITIS.

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Mediastinitis like inflammations elsewhere may occur in the acute or the chronic form. Acute simple mediastinitis is only of pathological interest as it cannot be reconized clinically. The acute suppurative form is extremely rare. The only case of this nature that I can recall in 13 years of hospital experience was that of an infant in Sir William Osler's service in The Johns Hopkins Hospital about the year 1904. Some of you may possibly recall the case, the main points of which were stridor, a croopy cough, dyspnœa and dysphagia, with an irregular pyrexia, and definite retrosternal dulness. The autopsy revealed tuberculous caries of the lower cervical and upper dorsal vertebræ resulting in an abscess which burrowed downward into the posterior mediastinum.

The chronic forms are of greater frequency at least clinically, and it is especially to this type that I wish to call your attention.

Chronic or, as it is sometimes called, indurative mediastinitis was first brought to our attention by Kussmaul in 1873. Occasional articles in the medical journals have appeared from time to time since then. H. A. Hare<sup>1</sup> in his essay of 1889 on affections of the mediastinum writes of this condition. Probably the most extensive contribution to the subject, however, is a monograph by Thomas Harris,<sup>2</sup> appearing in 1895, in which all the cases in the literature to date are abstracted, and in which a very full description of the symptoms and physical signs is given.

*Etiology.*—It usually follows an acute rheumatic pericarditis, but may also develop subsequent to fibrinous pleurisy, or in association with some other of the acute conditions of the chest. It may follow even an acute general infection, as scarlet fever or measles, without the history of any recognized pericarditis or pleurisy. Occasionally it is chronic from the

outset, secondary to a tuberculous focus of the mediastinal glands or of the adjacent lung. Tuberculosis is certainly a more frequent etiological factor than has been generally recognized. Both of our cases probably have a tuberculous basis.

Syphilis, too, has played an undoubted role in a small proportion of the cases. Syphilitic mediastinitis forms the topic of one of the recent French theses.<sup>3</sup> Sorel<sup>4</sup> takes the extreme view that the usual etiology of chronic mediastinitis is syphilis or syphilis and tuberculosis. Various infections of the bony framework of the upper chest may also be responsible for a chronic, indurative fibrosis of the mediastinum.

*Morbid Anatomy.*—Post mortem one finds a more or less marked increase of the fibrous connective tissue in the mediastinum, resulting in the matting together of the different viscera to one another, and in some cases to the chest wall. There may be in addition such marked pericardial and pleural adhesions that the entire thoracic contents are fused together.

The adhesions are often very firm and dense as emphasized by the term "indurative." Compression of the large vessels, particularly of the veins, is a frequent result. In several cases the superior vena cava has been occluded by the development of a thrombus behind the point of constriction. Osler<sup>5</sup> has reported such a case, and has collected four other cases from the literature in which a diagnosis of mediastinitis was made in association with thrombosis of the superior vena cava. In Osler's case there was established an extensive collateral venous circulation. As one might expect, there is frequently evidence of venous obstruction in the liver, spleen, and kidneys.

When an adhesive pericarditis is present there may result a form of pseudo-hepatic cirrhosis, first described by F. Pick,<sup>6</sup>



and characterized by an atrophic nutmeg-liver and subsequent ascites. If long continued Pick suggests that the typical "zukergussleber" and thickening of the peritoneum may result.

H. G. Wells<sup>7</sup> has described a true cirrhosis of the liver in cases complicated by calcification of the pericardium. Effusion into one or more of the serous sacs may be found.

**CASE I.—Clinical summary.** *No history of lues. Possible history of tuberculosis. Dyspnœa, cyanosis, swelling of the neck and face, distention of the superficial thoracic veins, gradual enlargement of the parotid glands, retrosternal dulness, mediastinal friction.*

L. F. Age 28. Occupation, machinist. Was referred to my office January 5, 1914, by Dr. C. C. Smead, of Newton, Iowa.

**Complaints.**—Swelling of the face and distention of the veins of the chest.

**Family history** was negative for tuberculosis. His wife and three children are living and well. One died at one and one-half years from some "brain fever." His wife had had one miscarriage between the second and third pregnancies without known cause.

**Personal History.**—Patient was born and bred in Iowa. For some years had been a blacksmith, but recently had to give up this trade owing to the heavy work it entailed. Admitted the use of coffee to excess, but always used alcohol most moderately. Has been a heavy user of tobacco, chiefly chewing. He admitted the usual diseases of childhood, as measles, chicken pox, and whooping cough. He denied absolutely lues and tripper. Had had no pulmonary or cardiac symptoms prior to the present illness. His mother had definitely told him that he was not a blue baby. His appetite was large, digestion good, and bowels regular. Maximum weight was 200 pounds.

**Present Illness.**—Began seven years before when at the age of 21 he first noticed cyanosis and swelling of the face and neck. Shortly afterwards he had a profuse hemoptysis, unassociated with cough. At about this time palpitation of the heart and intermission of the pulse became evident. There soon developed some cardiac pain and some dyspnœa which gradually increased in intensity. He now has slight orthopnœa at night necessitating the use of two or three pillows. At the age of 22 he had an attack of epidemic parotitis with a complicating orchitis. This he stated had no appreciable after-effect upon the swelling of the face. At about this time he first noticed dilated veins over the chest. At 23 he had pneumonia from which he was laid up one month. At 27 had a severe febrile illness of eight weeks' duration while on a visit to Missouri, which was diagnosed malaria but did not yield to quinine. His symptoms had been more pronounced since that illness. He had lost little or no weight, and was absolutely free from cough, sputum, fever, etc. He was still able to earn his living as a machinist, if he avoided extreme exertion. He had seen many physicians and one well-known consultant who made a diagnosis of intrathoracic struma.

**Physical Examination.**—Patient was a large, stout, healthy looking man 5 feet 10 inches in height, and 193½ pounds in weight. There was marked suffusion of the conjunctivæ and slight prominence of the eyes. The face, lips, ears, and fingers tips were markedly cyanosed and the latter distinctly clubbed. The facies were rendered additionally striking by the presence of bilateral enlargement of the parotid glands, which could be readily outlined and which extended up in front of the ear and down to the angle of the jaw. They were perfectly soft in consistency but a little tender. The lachrymal glands were also distinctly enlarged, but the submaxillary, sublingual, and accessory glands of the mouth were normal in every respect. The tonsils were distinctly enlarged and showed evidences of previous disease. The pupils were round and equal, and reacted promptly to both light and

accommodation. The thyroid gland could not be felt, but the whole neck seemed boggy and œdematous, and the veins were distinctly full and engorged. The lymph glands were nowhere enlarged. The thorax upon inspection was large and square, and deep. Scattered over the chest, both anteriorly and laterally, was a regular network of superficial venules, as well as many large tortuous veins. These appeared to anastomose with the abdominal superficial veins, which were perhaps a little fuller than normal, though not as strikingly enlarged. The veins of both arms, but more particularly of the right, were more prominent than usual. The expansion of the chest was a little restricted, and Litten's sign could not be seen owing possibly to the very abundant panniculus. The lungs were perfectly clear on percussion. The breath sounds were vesicular, and no rales could be heard even after coughing and deep breathing. The heart revealed no special area of visible cardiac impulse. The P. M. I. was just palpable in fifth intercostal space 10 cm. from the mid-sternum. The relative cardiac dulness began at the upper border of the third rib and extended 2 cm. to the right and 10 to the left of the mid-sternum. On percussion over the manubrium there was a distinct area of dulness corresponding to the anterior mediastinum. At the apex the heart's sounds were rather distant but perfectly regular. The first was muffled and somewhat toneless, but free from definite murmur. At the base the pulmonic second was much accentuated and tapping, while the aortic second was barely audible. No murmurs at the base. With the bell of the stethoscope over the manubrium and elevation of the arms above the head, a rough, crunching murmur became audible. The pulse was 76 to the minute, regular in both force and rhythm, of good volume, and normal wave. There was a systolic blood-pressure of 142 mm. of mercury. The vessel wall could not be felt. In comparing the two radial pulses they were found to be synchronous and equal. There was no tracheal tug, no hoarseness of the voice, but the larynx was not examined. The abdomen was large, with very thick, fat walls and fullness of the superficial veins. The edge of the liver could not be felt nor was it enlarged to palpation. The spleen was not felt. There was no evidence of ascites. The shins pitted on firm pressure, as in most stout individuals. The blood count revealed a hæmoglobin of 85% (Sahli); R. C. 5,120,000; W. C. 6200. Differential count: P. N. 79%; Ly. 13%; L. M. 3%; Trs. 7%. The urine was negative for albumin and casts. The Wassermann was negative in the blood on two successive occasions. A skiagram revealed a dense shadow in the mediastinum but no suggestion of an aneurysm.

The patient returned for re-examination on May 19, 1914, when no obvious change could be found in the above signs. He reported that early in March he had an attack of diphtheria, during which his face became "bloated like a toad," but this again subsided. He had gained somewhat in weight since last visit, reaching 193¾ pounds.

**CASE II.—Clinical summary.** *Acute lobar pneumonia complicated by empyema long unrecognized; resection of ribs and finally a thoracoplasty; persistent sinus, discharging pus and calcareous material; bronchial fistula; infiltration of one apex; no pressure symptoms; mediastinal friction rub; pulmonary osteoarthropathy, mastoiditis chronica.*

J. W. Male. Age 51. Farmer. Admitted October 2, 1911, to University Hospital. Clinical No. 345.

**Entrance Complaints.**—Cough and discharging sinus.

**Family history** negative for tuberculosis. Wife living and well. No pregnancies and no miscarriages.

**Personal History.**—Patient was a farmer of excellent habits. Denied both lues and tripper. Had mumps and pertussis in childhood. Measles at 21, diphtheria at 32. Denied scarlet, typhoid, rheumatic, and malarial fevers.

**Present Illness.**—Had always enjoyed excellent health until the onset of present illness. This began in November, 1909, with a



right-sided lobar pneumonia, following which he was in bed for three months on account of dyspnoea, fever, chills, and cough. In April, 1910, he was sent to Colorado with a diagnosis of pulmonary tuberculosis. In July, 1910, the correct diagnosis of empyema was at last made, a portion of one rib resected and a quart of pus evacuated. This gradually healed, but as the symptoms and signs persisted a second rib was resected in September, 1910. Following this the patient gained in weight and strength. In January, 1911, he developed an otitis media which in spite of repeated incision of the tympanum was followed by mastoiditis. In September, 1911, he was admitted to Dr. L. W. Dean's service at the University Hospital and a simple mastoidectomy performed which resulted in complete cure. On account of the cough, sputum, and discharging sinus he was referred to the medical clinic for examination on October 2, 1911. At this time the right side of the chest was found much shrunken and the lower half almost motionless, with a small sinus in the right lower axilla discharging a little thin, yellow pus. Signs of fluid were found in the lower right chest as well as a bronchial fistula. In addition over the apex of the left upper lobe signs of infiltration were present. The heart was not displaced. The sputum was negative for tubercle bacilli, on repeated examination. The blood examination was Hb. 75% (Sahli); R. C. 6,559,000; W. C. 5500. On November 2, 1911, several calcareous masses the size of a small pea were discharged from the sinus.

On December, 2, 1911, the patient left the hospital but returned in February, 1912, to the surgical clinic where Dr. Jepson did an extensive thoracoplastic operation, removing the anterior half of five ribs. After remaining in the hospital for six months the sinus still persisted though his bronchial fistula had closed and his general health was much improved. From time to time, however, after returning home, the patient would have periods in which "pus would be discharged through the bronchus," preceded by pain in the side, chills, and fever. From March to May, 1914, the bronchial fistula was practically closed, though when he assumed certain positions he could still hear the inspiration and expiration of air in the sinus. The sinus continued to discharge and recently a calcareous plate 2 x 1 cm. had been found in the wound. He had fallen from 154 pounds in November, 1911, to 130 pounds in May, 1914. He was therefore readmitted to the medical clinic on May 20, 1914 (clinic No. 1486).

*Physical examination* on May 21 revealed a somewhat emaciated white male of about 50 years. Face ruddy and sunburnt. Skin of chest covered with the brown scales of tænia versicolor. There was marked incurvature of the finger nails and clubbing of the finger tips, with definite hypertrophic bone changes of both radii. There was no fullness of the superficial veins of the chest or uppers. Thorax was much deformed from the small, shrunken, flattened right side from which the anterior half of the fourth to the eighth ribs had been removed. In the right anterior axillary line was an old sinus discharging a moderate amount of thin pus: by reflected light the movements of the right half of the diaphragm could be seen. Injection of this with bismuth paste revealed a small, forked shadow directed upwards towards the root of the right lung. The percussion note was resonant over the right front from the apex to the fourth interspace, over which area the breath sounds were harsh, almost bronchial, and were accompanied by fine, moist rales at the height of inspiration, while spoken and whispered voice sounds were increased. Posteriorly over the upper lobe the note was dull to the level of the spine of the scapula, the breath sounds were harsh and accompanied by an occasional fine, moist rale. Over the lower front and back the note was dull and breath sounds much enfeebled. No evidence of a bronchial fistula. The left lung was hyperresonant throughout, the breath sounds loud and intense, while everywhere could be heard medium, moist rales. The heart dulness was not displaced, extending only 11 cm. to the left of mid-sternum. The heart

sounds were loud and regular and free from murmurs. No pericardial and no pleural friction could be heard but on placing the stethoscope over the manubrium and elevating the arms a loud, crunching friction could be heard similar to that of Case I. The skiagram revealed a uniform, normal, mediastinal shadow. The pulse was 64, blood-pressure 90 mm., synchronous and equal in the two radials. No inequality of the pupils. No hoarseness or aphonia. The abdomen was negative except for some tenderness and rigidity over the right epigastrium where there was a dull note extending downwards for two finger breadths from the costal border. The edge of the liver could not be felt. This suggested a possible subdiaphragmatic abscess. The blood revealed: Hb. 88% (Sahli); R. C. 5,500,000; W. C. 11,600, of which P. N. 54%; Ly. 41%; M. 2%; Trs. 2%; Eos. 1%. Wassermann negative. The urine was negative and there was no sputum. The temperature ranged between 99 $\frac{1}{4}$ ° and 98°.

No further evidence of a subdiaphragmatic process being found the patient was discharged on May 27, 1914.

*Symptomatology.*—The symptoms are chiefly cardiac in origin and consist of dyspnoea, cyanosis, and dropsy. Dyspnoea is a very varying factor and is usually only present on exertion, except in cases with associated pericardial adhesions and subsequent dilatation of the heart. The cyanosis and oedema are often pronounced and present a startling picture. Not only may the features be discolored and bloated and the face swollen, but the eyes may be prominent and staring, as if starting from their sockets, and even the conjunctivæ may be injected, suffused, or oedematous.\* The neck, too, may be obviously enlarged and tumid-looking, and has in some instances such a spongy or elastic feeling as to suggest a diagnosis of a very vascular struma. The cyanosis is more or less constant, but is usually increased by exertion or by stooping over.

The most striking objective symptom is often a marked distention of the superficial veins of the neck, chest, and even of the face and upper extremities. There is invariably in such a case the establishment of a compensatory circulation as is evidenced by the tortuous, prominent, superficial, epigastric veins extending upwards from the groin and the sides of the abdomen to anastomose with the axillary and mammary veins. This was present to a remarkable degree in Osler's<sup>5</sup> case and to a marked degree in my Case I.

Ascites is very apt to occur before the development of a general anasarca, due to a chronic peritonitis from venous congestion, or possibly to an associated hepatic cirrhosis as has been described under the morbid anatomy.

Pain behind the sternum is by no means a constant feature, but has been noted in certain of the cases. Oesophageal symptoms, as dysphagia, and tracheal symptoms, as stridor, brassy cough, etc., are rare. Laryngeal paralysis may occur. An interesting suggestion has been offered by A. Adam\* to explain the frequency of recurrent laryngeal paralysis in acute pericardial and cardiac conditions, which was formerly referred to the mechanical pressure effect of the auricle or of the pericardial fluid upon the nerve. He believes that neither of these explanations is plausible, and states that one often finds a spreading of the inflammation from the pericardium to the mediastinum, with callous strands and firm, fibrinous adhesions in the mediastinum. In four cases, two with de-



compensated mitral disease and two with serous pericarditis, a chronic mediastinitis was found in association with paralysis of the recurrent nerve from involvement of the latter in the scar tissue, or possibly by extension of the inflammatory process to the nerve itself.

The thoracic duct may be obstructed and result in the development of a chylous ascites, as in a case of Comey and McKibben<sup>10</sup> in which a tuberculous process extending from the apex of the left lung involved the thoracic duct in its scar tissue.

*Physical Signs.*—*Inspection* may reveal some deformity of the thorax. According to Oliari,<sup>11</sup> in cases developing in childhood, the anterior part of the chest in the region of the sternoclavicular joints and the manubrium may become depressed as a result of impairment of the function of the affected bronchi. Much more frequently there is an inability to expand the chest to its full extent.

*Palpation* reveals little or no change except when there is an association of infiltration of the lungs or an effusion into the pleural cavities.

*Percussion*, on the other hand, may reveal a dull note over the manubrium and the interscapular region from the presence of dense fibrous adhesions and sometimes from the enlargement of the mediastinal glands.

*Auscultation.*—Apart from the various murmurs of the possible associated endocarditis Siebert<sup>12</sup> and others have described a loud, blowing, continuous systolic murmur localized to the second right interspace close to the sternum, independent of the cardiac cycle, and increased by both deep breathing and by holding the breath. This murmur is due to the stenosis of the superior vena cava from compression by enlarged glands or other solid tumor, and we might add, possibly, by bands of connective tissue.

In addition to this, auscultation may reveal a very important sign, first described by George Perez.<sup>13</sup> This consists of a rough, creaking, to-and-fro friction audible by stethoscope over the manubrium when the arms are moved upwards and downwards as in the act of artificial respiration. This sound can be readily differentiated from that heard in muscular individuals submitted to the same test, when a finer, more crepitant noise can be heard, not unlike the muscle rale heard elsewhere over the thoracic musculature. Little or no attention seems to have been paid to this sign, as I found only a passing reference made to it in one of the systems of medicine.<sup>14</sup> We have tried it out in a number of presumably normal cases, 10 in all, in which at the most only the fine muscle rale could be elicited. In several other forms of mediastinal disease it has also been tested, as aneurysm of the transverse arch of the aorta (one case), atheroma and dilatation of aorta (one case), mediastinal Hodgkin's disease (one case), lymphatic leukemia with marked involvement of the mediastinal glands (one case), apical tuberculosis (four cases), sero-fibrinous pleurisy (one case), healed empyema (one case), in all with negative results. In addition to the two cases above reported there was a suspicious, crunching sound audible over the manubrium and body of the sternum in the later stages of a case of car-

diorenal insufficiency. Autopsy revealed no mediastinitis but an acute, fibrinous pleuropericarditis.

In the first of the two positive cases it was astonishingly loud and clear and helped to exclude a mediastinal tumor which had been suggested by a previous consultant. In the second case no doubt could be entertained as to the probable presence of an indurative mediastinitis, as the long-standing empyema with the discharging sinus extending towards the root of the lung would so easily lead to a fibrous obliteration of the mediastinum and its contents. Though neither case has come to autopsy we feel that there is little doubt, from the history and other signs present, of the diagnosis of mediastinitis. In both of these the friction was striking and I believe a sign that must be regarded as of distinct value in the diagnosis of this affection.

*Accessory Signs.*—Various abnormalities in the cardio-respiratory movements, analogous to those found in mediastinal tumor and aortic aneurysm, have also been demonstrated by a special recording apparatus. Seibert gives tracings of his cases illustrating increased cardiopneumatic motion, and suggests that shrinkage or fibrosis in the mediastinum may offer very favorable conditions for the oncometric propagation of the cardiac and vascular motion. He admits further observations are necessary to decide the importance of such tracings in the diagnosis of mediastinal disease.

In more marked mediastinal fibrosis the "pulsus transversalis" or laryngeal pulse occurs, as evidenced by a marked visible pulsation of the larynx and trachea synchronous with the heart. It is due to the increased aortic impulse or to the intimate contact of the aorta with the tracheo-bronchial apparatus brought about by the fibrous adhesions. This is not to be confused with the Oliver-Cardarelli phenomenon or tracheal tug, which can be elicited on palpation when the trachea is put on the stretch in many cases of aortic aneurysm, but also in certain cases of indurative mediastinitis when the trachea and aorta are firmly bound together.

Wenckebach considers as an important sign inspiratory swelling of the veins in the neck due to the impeded emptying of the systemic veins by fibrous adhesions. This sign is in the opinion of many of very doubtful value. The "pulsus paradoxus," or inspiratory intermission of the pulse, is often absent in cases of indurative mediastinitis, and may occur in other conditions, or, in a perfectly normal subject.

*Differential Diagnosis.*—The differentiation of other conditions of the mediastinum is not always an easy matter, but the following points will help to decide:

1. Aneurysm of the thoracic aorta. In this condition one finds a localized impulse or sac with an expansile pulsation discernible either on palpation or by fluoroscopy. A history of syphilis or the presence of any of the stigmata, as a gumma or a positive Wassermann reaction, are further aids. A ringing character to the aortic second sound should also make one suspicious. All the pressure symptoms, particularly those upon the trachea, recurrent laryngeal, and sympathetic nerves are present, while tortuosity of the superficial veins and œdema



of the face and neck are rare, though they may occur as pointed out by Osler.<sup>15</sup>

2. Solid tumors of the mediastinum may be suspected in an adult with a history of pain or distress in the sternum, a constant or paroxysmal, or a brassy cough without sputum, an area of retrosternal dullness, dysphagia, inequality of the pupils or of the pulses, and evidences of venous obstruction. The absence of expansile pulsation and of the ringing character of the aortic second sound are to be noted.<sup>15 16</sup> Korányi<sup>17</sup> has found that the percussion note over the vertebral spines is normally flat over the seventh cervical becoming gradually more resonant from the first to fifth dorsal, while from the sixth to the ninth the note is full, clear, and non-tympanic. In cases of solid tumors of the mediastinum, whether from neoplasm or tuberculous glands, the flatness continues below the eighth cervical and modified resonance extends to a lower level than normal. Further on auscultation, increased breath sounds, and bronchophony may be present in this region.

3. Abscess of the mediastinum will present less difficulty, as a history of traumatism with dullness or even light percussion over the sternum, and the presence of a fever of a hectic type will be important suggestive facts.

*Treatment.*—Naturally the treatment is largely symptomatic, though possibly cardiolysis may be tried in selected cases.

Recent literature offers encouragement. Rives,<sup>18</sup> in 1912, reports some success with cardiolysis, more particularly in the improvement of the cardiac function with disappearance of the dyspnoea and the passive congestion of the liver and spleen. Wulz<sup>19</sup> also reports the successful removal by Hofmeister of a mediastinal tumor made up of a remarkably developed connective tissue matrix containing numerous submiliary tubercles. The introduction of the negative pressure chamber and the positive pressure apparatus has rendered operative pro-

cedures upon the mediastinum comparatively safe, and the future no doubt will reveal a marked increase in the list of symptomatic cures.

*Conclusions.*—1. Tuberculosis plays a very important role in the etiology of chronic mediastinitis.

2. One or more of the pressure phenomena of mediastinal tumor and aortic aneurysm may be present in this condition.

3. Perez' mediastinal friction was present in our two cases, and may prove of diagnostic value.

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## TERTIARY SYPHILIS OF THE LIVER.

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My particular interest in this subject goes back a good many years to the time when I was the resident in charge of the medical patients in the private wards of this hospital. A patient was admitted who volunteered the diagnosis of his own condition as cancer of the stomach. He had lost considerable weight, looked very badly, was anæmic, and presented a very definite nodular tumor in the epigastrium. After studying him I felt very doubtful of his having carcinoma, but was uncertain as to what he really did have. The diagnosis made by Dr. Osler was syphilis of the liver, and such the results of treatment proved it to be. The nodular tumor disappeared very quickly, the patient gained rapidly in every way, and has been in excellent health since then. The study of this case interested me in the subject and I have followed it as closely as possible since then. I have now a series of 70 cases, and to-day I wish to present some of the points which have specially impressed me

rather than enter into a detailed study of the whole subject. The results of the study of 56 cases in the service of this hospital I have reported previously.<sup>1</sup>

Certain points have impressed themselves, in the study of this subject. The first is the relatively slight attention which has been paid to it. The literature on syphilis is perfectly enormous, but the articles dealing with syphilis of the liver are comparatively few in proportion. The second point is the relative frequency of the condition. It is difficult to obtain any figures which are of much value, but my personal impression is that tertiary lesions occur fully as often in the liver as in the nervous system. The third point is the ease of diagnosis in the majority of cases when one knows about the condition. The fourth point is the satisfactory result of treatment if the

<sup>1</sup> Amer. Jour. Med. Sc., 1912, CXLIV, 625.



diagnosis is made in good time. Some of the more striking features of the series are as follows:

As regards *etiology*, it is a disease particularly of adult life, the largest number of cases occurring between the ages of 20 and 40 years. The largest number in one decade occurred between the ages of 30 and 40 years. A comparatively small number of cases occurred after the age of 50 years. It is not a disease of advanced life.

In reference to *race*, an undue proportion of the cases occurred in the colored race, and I find this to be as true in Philadelphia as it was in Baltimore. A surprising number of colored women are affected; the number is larger relatively than of the colored males, and a great deal larger relatively than of the white females.

Of any possible other factor, *alcohol* seems to take the first place. Excluding the cases which occurred below the age of 20 years, four in number, there were only five patients in the series who did not give a very definite history of the free use of alcohol; probably a third of the series might be described as having used alcohol to excess. From this it must not be inferred that syphilis attacked a cirrhotic liver in these cases, but the inference seems to be that a liver which has handled large amounts of alcohol is apparently more likely to become the seat of a luetic process.

As regards a definite history of syphilitic infection, excluding the late congenital cases, there was a positive history of a primary lesion in half the series and in a certain number of others there were extremely suggestive features. In all the cases of the late congenital form there was a history of the disease which seemed definite in one or both parents.

*Clinical Picture.*—The variations at first sight suggest a confusing diversity, but when a series of cases is studied, it is possible to simplify them to a considerable extent. One important point is to separate the symptoms from the liver condition from those due to other associated disease. It is evident that a patient may have syphilis of the nervous system as well as of the liver, or that he may have cardiac or renal disease, or extensive arteriosclerosis. The features of the other disease may predominate and obscure those due to the hepatic changes.

Of the complaints which brought the patient to seek advice the most common was swelling of the abdomen, and next in frequency abdominal pain. Loss in weight occurred in many cases and was often extreme. The complaints ranged over a wide field—jaundice, vomiting, fever, sometimes with chills, and swelling of the legs were among these. In one group which is of particular interest the occurrence of prolonged fever was the striking manifestation. In several of the patients the diagnosis of tuberculosis had been suggested, and one patient had spent two years in a sanatorium with a diagnosis of tuberculosis. If chills occur in addition to the fever, it is very evident that a mistaken diagnosis may readily be made. The *duration* of the symptoms before the patient came under observation showed a wide variation. The shortest was a period of three weeks. This patient came with very marked changes in the liver and it seemed impossible that they should have been brought about in such a short time, but the evidence

was very definite that the patient's health had been perfectly good previously. The longest duration of symptoms was 11 years. The majority gave a history of illness varying from three to 18 months. A striking feature in this connection is the variation in the symptoms from time to time in many of these prolonged cases. This is sometimes associated with the occurrence of ascites. Several of the patients had had attacks of ascites for which tapping was required, after which there had been marked improvement for a time. Several of the patients gave a history of alternate periods spent in bed and up and about and at work. I am not aware of any other condition in which we have a history of recurring attacks of ascites with practical recovery in the intervening periods.

A rather striking feature in the history of the patients was the occurrence of *pain*, variously referred to the upper abdomen, to the upper epigastrium, or to the upper right quadrant. It was rare to have the pain described as being in the back.

*Clinical Features.*—Certain general conditions were marked and attracted attention. One of these was the loss in weight. This was marked in half the cases of the series and in a number of them was extreme. If with this there is jaundice and some anæmia, the patients present a picture quite suggestive of malignant disease. *Jaundice* occurred in just about half the series. Another general feature was the occurrence of *fever*, which was present in all but eight cases of the series. In the majority of cases the temperature record was not specially high, rarely going above 101°, but in some there were elevations to much higher figures, in one case to 106°, and with this there were repeated chills. It is easy to understand how the occurrence of chills and fever may suggest various diagnoses, such as malaria or abscess of the liver. Syphilis should always be kept in mind as a possible cause of continued fever for which there is no definite evident cause.

The *blood* showed a secondary anæmia, which, however, was not very marked. The average hæmoglobin estimation was about 70 per cent and the red cell count about 4,500,000. The leucocytes were usually about normal and no case showed leucocytosis. The differential count did not show any special abnormality. *Ascites* occurred in 27 cases of the series, but only 13 required tapping, which emphasizes the possibility of the rapid disappearance of the ascitic fluid under proper treatment. A positive Wassermann reaction was given by the ascitic fluid in one case. There are several instances in the literature of this finding.

As might be expected the changes in the liver and spleen were of particular interest. The *spleen* was palpable in half the patients; in a number of these the enlargement was very marked, in some instances the spleen extending almost to the navel. This had led to a diagnosis of splenic anæmia in several cases. In reference to the changes in the liver itself, the great majority showed some marked alteration, and a study of this showed that most of the cases fall into one of three groups:

(1) The liver shows general enlargement, in the majority of cases the organ being comparatively smooth. There were 27 cases in this group.



(2) The group in which the liver shows definite nodules. There were 21 cases in this group.

(3) The group in which the liver shows marked general enlargement and also very marked prominences. This occurred in 11 cases.

The remaining cases of the series could not be classified definitely, as they showed features of two of these groups.

It is evident that without a knowledge of the condition these changes in the liver may lead to an erroneous diagnosis; for example, in the group with general enlargement, chronic passive congestion or amyloid disease might seem to explain the condition. Hepatic abscess might be considered, especially if the patient has high fever and chills. In the second group, with the nodular enlargement, malignant disease is specially suggested, but in others the changes may be regarded as due to tuberculous peritonitis. In the cases with the large round prominences, malignant disease is most likely to be considered.

*Diagnosis.*—In reference to mistakes the cases may be put in three groups:

(1) Those in which the hepatic features are missed entirely. A number of things may contribute to this; for example, if cerebral syphilis is present as well, all the attention may be directed towards this and the involvement of the liver overlooked. If the patient has cardiac disease, as many of them are likely to have, it is easy to regard the enlargement of the liver as due to passive congestion. The mistake which is most removed from the truth is to make a diagnosis of tuberculosis, as was done in several of this series. It is evident that this error is particularly likely to be made in the patients who have continued fever over a long period of time.

(2) The group in which abdominal disease is recognized but its nature is not determined. Here tuberculous peritonitis, carcinoma of the peritoneum, and carcinoma of the stomach are the most probable diagnoses. With the diagnosis of carcinoma the duration of the disease may be the first thing to arouse suspicion.

(3) In this group the hepatic disease is recognized but its nature is not determined. The common error is to regard the condition as an ordinary cirrhosis of the liver; abscess of the liver and gall-stones have also been suggested. Several patients of this series had been operated upon for supposed gall-bladder disease.

There are several points which deserve attention as aids in the diagnosis. It is important to realize the frequency of the condition and to know something about the clinical picture. One feature, which is always suggestive, is that the left lobe of the liver is often involved to a much greater extent relatively than the right lobe. This should always suggest the consideration of syphilis. Another point to keep in mind is that a history of ascites which subsided spontaneously or disappeared after tapping to reappear sometime later should excite suspicion. The importance of examining the patient immediately after tapping also deserves emphasis. It may be possible only at that time to have an opportunity of palpating the liver in a satisfactory way.

Another point worthy of attention is the therapeutic test. Naturally we hesitate to place much dependence upon such a test but in this disease it is often confirmatory. This is usually strikingly shown in the temperature chart. After iodide is taken a remarkable feature is the rapidity with which the temperature falls to normal. In the majority of cases this occurs within two days and it rarely takes longer than five days. The same marked effect is sometimes seen in the liver and the enlargement may disappear very rapidly.

Early diagnosis is very important. For the patient it means the probability that he will recover entirely, whereas if the condition is allowed to persist, cirrhosis will probably result and then the damage is beyond repair. A correct diagnosis is also important for the surgeon, as it may save him from doing a needless abdominal exploration. Several of the patients in this series have been operated on under various diagnoses. One patient seen recently had two abdominal sections by different surgeons, one making the diagnosis of gall-stones, the other confessing himself puzzled, and making an exploration for diagnosis.

*Treatment.*—As regards the essential liver condition, this may be summed up in one word—"iodide." Under it alone the hepatic condition may clear up absolutely. Several patients in this series were given salvarsan, but without any very apparent effect on the liver itself. A general syphilitic infection demands treatment with mercury or salvarsan, or both, but the hepatic condition yields particularly to the use of iodide. The dosage does not require to be very large, and in the cases of this series rarely went above 60 grains a day. Tapping should be done whenever the amount of fluid demands it.

## THE INFLUENCE OF DIETING UPON THE COURSE OF CANCER.

By PEYTON ROUS, M. D.

The subject upon which I shall speak to-day—with the great privilege of speaking before this audience—may seem to many of you to have a merely curious interest. Indeed, *a priori* the influence of dieting upon the course of cancer may not seem worth even curiosity. For true it is that throughout time countless people with cancer have eaten and drunk all sorts of things, have been stout or been thin, and yet have ended by dying of their disease. Perhaps, then, it will be

well for me to take up some of the general aspects of my subject.

We are accustomed to think and speak of cancer, according to a definition duly remembered, as one of the autonomous new growths. Certainly it is autonomous enough to prove fatal to the patient. Yet you will agree with me that in its general characters the cancer cell is far from showing independence. Apart from its capacity for unlimited growth



without differentiation it has almost no distinctive peculiarities. Recent cancer research with animals has made this very evident. So far as we can tell the cancer cell secretes no specific enzyme, gives forth no specific toxin, produces no immunity reaction in the body that can be used with certainty for diagnostic purposes, and has few features that suggest methods of therapeutic attack. The most successful, non-surgical methods of treating cancer are based on quantitative, not on qualitative, differences between the cancer cell and normal cells. The Roentgen ray and radium act selectively on the cancer cell simply because it is somewhat more sensitive than normal cells.

All this being true, is it not possible that, even as regards growth, cancer is less independent than we are given to suppose; and that bodily conditions which affect normal tissue generally will also affect cancerous tissue? There are certain clinical indications that this is true. Some diseases, notably erysipelas, which profoundly affect the whole organism, may affect a cancer so adversely that it becomes stationary or retrogresses. The observation has been repeatedly made that in withered, old persons cancer grows slowly. And thus one comes to ask whether dieting or special diets may not exert an important influence on cancer. To put a concrete case: When a cancer has been removed that is likely to recur should the patient be fed to plumpness? Is it not possible that by keeping him thin, or underfeeding him so that he loses in weight, a recurrence of the tumor will be delayed?

Manifestly such questions can be answered only by experiments with animals. And now that the status of rat and mouse tumors as true neoplasms is assured this can be readily done. Moreschi was the first to take up such work systematically. He underfed rats so that they lost in weight, and found that grafts of rat tumor had poor success in such animals as compared with full-fed controls. Soon after the appearance of his paper, experiments were begun at the Rockefeller Institute. But though we were able to confirm Moreschi's findings as regards tumor grafts, it proved quite another matter to influence tumors already ensconced and vascularized. A rat carcinoma was found to grow quite as well in rapidly emaciating animals as in those gaining weight on full diet. That a graft introduced into an alien, normal creature should prove less resistant than a tumor which has the organism of the host under its thumb, so to speak, is scarcely surprising. But, unfortunately, it is with the latter condition that one has to do in human beings. In several recent researches this point seems not to have been taken into sufficient account. The investigators have found that special diets exert an adverse influence on cancer grafts in normal hosts. But experiments with tumors already growing have been few and inadequate.

Last year, Dr. Linda Lange and I attempted to determine whether recurrences and metastases of large tumors removed at operation may not behave like grafts in that they are sensitive to dietary influences. Metastases are certainly to be considered as grafts, at one time in their development, though with the advantage on their side that they are autotransplanta-

tions in an animal already the subject of cancer. For our first experiments transplanted tumors were used; but it was soon found that they were not a fit material. I have spoken of the lack of immunity phenomena in animals with cancer. This had reference only to "spontaneous" cancer. In normal animals to which cancer is transferred by grafting there often develops a marked resistance, directed apparently against the growth simply as alien tissue. It may, and frequently does, cause the rapid retrogression of large tumors. It brought much confusion into our experiments, and we came at length to realize that in order to obtain facts for a generalization about spontaneous tumors observations on such tumors would be necessary.

Spontaneous carcinomata are fairly common in the white mouse. Within a short period more than 130 were obtained, all of them tumors of the breast in old females. They were diverse in their histology. For the experiment, half of the tumor animals were underfed so that they lost in weight; half, full-fed; and by a uniform technic the growths were removed save for a small bit. The vessels leading to this bit, which was left to insure a recurrence, were disturbed as little as possible. In each animal two subcutaneous implantations were made of its own tumor. These may be taken to represent in some sort disseminations at the time of operation. The feeding was continued as before and the animals kept under observation for five weeks, a period in the mouse's life equal to about three years in that of a human being—if any such comparison is permissible.

The results were striking. During the five weeks of observation, recurrences appeared in 83 per cent of the full-fed control mice, and in only 41 per cent of those underfed and losing weight at the time of operation. The grafts grew in 68 per cent of the controls and in 41 per cent of the underfed hosts. Evidently restricting the diet has a very marked influence to delay the reappearance of spontaneous mouse tumors.

A word should be said as to the diet. The controls were fed on grain and bread and milk. The experimental animals received Sweet's modification of one of the foods which Mendel and Osborne devised in the course of their study of the requirements for normal growth. The food in question is sufficient for the day-to-day needs of rats, but fails to suffice for their growth, because of its lack in certain amino-acids. Rats kept upon it remain healthy but never grow up. Sweet was able to prevent the development of tumor grafts in mice by putting them, previous to inoculation, on his modification of the food. We combined a use of it with underfeeding in the idea that perhaps thus more marked effects might be obtained. But special experiments have shown that our results are to be attributed solely to the underfeeding and resultant loss of weight, and not to the character of the food.

The treatment was drastic. The best results were obtained with animals losing weight rapidly at the time of operation. The average loss in weight at the end of the five weeks of observation was 24 per cent. But as the adult female mouse is a



fat, little creature with small bones and an abundant panniculus the emaciation was less than one would suppose.

No cures were effected. In underfed animals put again on full diet a rapid recurrence with growth of the grafts was the rule. In the light of this fact the quiescence of the tumor during the period of dieting can hardly be attributed to processes of resistance. We are inclined to attribute the results in part to direct starvation of the cancer cells, in which they shared with the other cells of the host. There is evidence that in far greater part they were due to a retarded formation of the connective tissue scaffold which furnished blood-vessels and support to the tumor. A very few tumors, and these the most malignant, are able to grow continuously without such a scaffold—to live, so to speak, off the country which they invade. Most require a vascularizing stroma, which is supplied by the host's tissue. In the underfed host, as we have shown by special experiments, proliferative processes take place slowly. Wounds require a long time to heal and an inert foreign body, such as agar-agar, is only tardily

organized. It is easy to see why the development of tumors dependent on a supporting stroma would be slower in such animals.

Whether recurrences and the development of metastases in human beings can be influenced by underfeeding is not to be foretold. Important in this relation is the fact that a small percentage of the tumors in the underfed mice of our experiment—and these the most malignant ones histologically—recurred with a rapidity unexcelled by any of the tumors in full-fed animals. Here the end result of the treatment was a distinct injury, for the host was prematurely emaciated and the development of the growth was unchecked. It is quite probable that the same thing would be true of some human tumors. And to underfeed a cancer patient so that he loses weight is to incur many other dangers. I do not wish, then, to be taken as an advocate for underfeeding in the palliative treatment of cancer. Yet, to judge from the experimental evidence, it might do good in special cases.

## RECENT DEVELOPMENTS IN RELATION TO THE STUDY OF TROPICAL MEDICINE IN THE UNITED STATES.

By RICHARD P. STRONG, M. D., Sc. D.,  
*Professor of Tropical Medicine.*

It seems appropriate that I should address you on this occasion upon the subject of some of the recent developments in relation to the study of tropical medicine in the United States. The Johns Hopkins Hospital and Medical School took a very early interest in the question of tropical medicine in this country, and a number of important researches relating to this subject were performed by members of the staff of this institution. As is well known, Sir William Osler in 1890, in the United States, first demonstrated amœbæ in the stools and liver abscess pus from a patient who had contracted the disease in Panama. Dr. Thayer's important studies and publications in relation to malaria and the malarial parasites, which were also the first of this nature to be made in America, are too well known to make seem superfluous any detailed reference to them at this time. Let us consider some of the investigations which were carried on in Dr. Welch's laboratory in relation to this subject. The monograph of Councilman and Lafleur upon the pathology of amœbic dysentery is one of the most valuable contributions which has appeared in the literature upon this disease. Again Councilman and Abbott's work, and that of Barker, upon the pathology of pernicious and cerebral malaria threw much additional light upon these subjects. The earlier students in this medical school—with such examples of achievement before them in relation to tropical disease, and with the remarkable inspiration given them by the members of the very unusual staff of this institution at that time, together with the placing at their disposal for study the valuable tropical material available in the wards—could not fail to be impressed with the importance of the subject, and in a number

of instances became especially interested therein. The researches of Opie and MacCallum upon *Halteridium*, the discovery of MacCallum of the function of the extruded microgamete of the malarial parasite, and the important investigations of Thomas R. Brown upon eosinophilia in relation to trichinelliasis and other nematodal infections, are examples in point. These gentlemen were all fourth-year students here at the time these observations were made. I, among this group of earlier students—particularly through the enthusiasm inspired by my instructors and through observation of the cases of tropical disease assigned me for special study by Drs. Osler and Halsted, and through the truly fascinating way in which the pathology of these diseases was demonstrated and taught by Dr. Welch—became so interested in the subject that I determined later to specialize in it. I would that I could find words to express the gratitude I owe and feel to my former professors and instructors of this institution for the inspiration for this work which came from them. As we come back here to-day I think many of us realize as never before what this institution means to us. We are not what we ought to be, or perhaps hoped to be, but from a medical standpoint, at least, we are, largely, what we are, through the influence of Johns Hopkins.

With the territorial expansion of the United States begun in 1898, and with the subsequent acquisition by our government of a number of tropical and subtropical possessions, new demands arose for an accurate knowledge of the diseases prevailing in these countries and for their prevention, and in many of these problems students and members of the staff of this institution took an active part.



At the beginning of the year 1899, a laboratory was established in the Philippine Islands, and later a board of medical officers was created there by the Secretary of War for the study of tropical diseases. This laboratory came to be known as the Army Pathological Laboratory of Manila, and it performed all the clinical and pathological laboratory examinations for the various hospitals in Manila and the vicinity. Original investigations relating to the prevailing diseases of the islands, and particularly to the various forms of dysentery and diarrhoea and intestinal parasites encountered there, were also carried on at this laboratory. Subsequently, in 1903, the director of this laboratory became the Director of the Biological Laboratories of the Bureau of Science,<sup>1</sup> when that institution was established, and the work of the Army Laboratory was taken over by the latter institution and the scope of it greatly extended. The researches carried on in the Biological Laboratories have become widely known particularly from the publications made from them in special reports and in the medical and biological sections of the *Philippine Journal of Science* published from that institution for the past nine years.

In the spring of 1899 The Johns Hopkins University and Hospital again demonstrated its interest in tropical medicine by sending an expedition to the Philippine Islands for the investigation of the prevailing diseases there. The members of the expedition were Drs. Flexner and Barker and Messrs. Flint and Gay, the last two being fourth-year students in the medical school here at the time. The expedition was a very successful one and will be particularly remembered by the importance of the studies which were carried on in relation to the subject of bacillary dysentery. Dr. Flexner's investigations carried on then and subsequently, and those of his pupils, particularly of Gay, are also thoroughly familiar to the members of an audience of this nature, and the great value of these discoveries has become generally recognized. Drs. Barker and Flint after leaving Manila also made observations relating to the bubonic plague situation in India.

Our military and governmental operations in Cuba had brought the United States face to face with the problems of combating yellow fever in that country, and here again this institution and the medical school played a very active part in this campaign. Dr. Walter Reed, the president of the commission appointed to investigate this disease, was a pathological assistant in the hospital in 1889-1890, and it was in the halls of this institution that he received instruction in the clinical examination of the blood from Dr. Thayer. He was also a pupil of Dr. Welch, from whom he was frequently in receipt of counsel and advice in many of his studies. Dr. Lazear, another member of this commission who had previously done admirable work also upon malaria, and who fell a martyr and gave his life to the cause, was a member of the staff of this hospital at the time. While the subject is one which must be very familiar to you, nevertheless, I feel I should again emphasize the great importance of the researches

of this commission. In the city of Havana alone nearly 40,000 people perished from yellow fever between 1853 and 1900. In 1900 at the instigation of General Leonard Wood, the United States Government introduced modern methods of preventive medicine based upon the discoveries of this commission, and but a single case of yellow fever has occurred there since 1907. Moreover, our ideas regarding the quarantine of the disease were completely revolutionized, and, as is well known, it has been completely banished from the Canal Zone, Panama, and other localities, largely through the discoveries made by this commission. Certainly these discoveries rank with the most important of modern scientific medicine.

Other members of the staff of the hospital and school have labored in the field of tropical medicine, and the names of Calvert, Woolley, Bean, Sellards, Gilman, Andrews, Bowman, Hammack, Duval, and Bloombergh in the Philippine Islands, of Whipple, Herrick, and Winn in Panama, and of Duval in New Orleans, are familiar to many of you. During the past summer months Drs. Moss and Guthrie have also entered upon the study of tropical medicine and have carried on investigations in Limon, Costa Rica. Johns Hopkins has just reason to feel proud of many of the achievements of her students in tropical medicine; and the work which has already been accomplished by them should serve as an example of some of the opportunities which have been open to students in this field.

With our gradually increasing knowledge of tropical medicine it became evident that special training was advisable or necessary for those who desired to treat or to carry on investigations relating to tropical diseases, and schools of tropical medicine came to be established in different countries. In Great Britain, two schools of tropical medicine were organized. The one in London, which has been practically directed by Sir Patrick Manson since its beginning in 1899, owes its origin largely to him and to the Right Honorable Joseph Chamberlain, who, while Secretary of State for the colonies, advised the establishment of such an institution with the object of affording instruction in tropical medicine to medical officers in the colonial service of Great Britain. The London school of tropical medicine is now recognized as a school of the University of London. The other school of tropical medicine in Great Britain, situated in Liverpool, which has been under the direction of Sir Ronald Ross, was founded in 1898 by Sir Alfred Jones for the purpose of promoting the study of tropical medicine by the investigation of diseases in tropical countries, and to provide suitable training for medical officers and others proceeding to the tropics. This school was formally opened by Lord Lister in 1899, and a year later received official recognition from the government by being authorized to supply the obligatory course of instruction for colonial medical officers proceeding to tropical countries. In Hamburg the Institut für Schiffs- und Tropenkrankheiten, presided over by Professor Nocht, was also established in 1900. France, Austria, and Italy have also established schools of colonial or tropical medicine.

In the United States, notwithstanding the growing impor-

<sup>1</sup> The writer served as director of this institution from its origin until February, 1913.



tance of the subject and the opportunities connected therewith both on account of our acquisition of tropical and subtropical possessions and of our greatly increased commercial relations with many other tropical countries resulting from the opening of the Panama Canal, our universities have been very tardy in regard to supplying students with adequate instruction and preparation in tropical medicine.

A number of medical schools have for several years announced in their catalogues instruction in tropical medicine as a part of the curriculum, but such instruction has been sometimes, at least, very inadequate. Tulane University, however, planned much more extensive instruction in this subject and stimulated work of this nature in the United States. Other schools have also extended their courses in tropical medicine. Finally, Harvard University, recognizing, on account of the increased intercourse with and interest of the United States in the tropics, the importance of providing proper instruction for students and opportunities for research work in the subject, established in 1912 a Department of Tropical Medicine with this end in view. During the present year this department has been organized into the Harvard School of Tropical Medicine. This school aims to give adequate instruction to physicians who intend to practice where tropical diseases are prevalent or occasionally encountered, to those who desire to accept positions in the government medical or sanitary service, to those who wish to carry on original investigations relating to tropical diseases, or to those who wish to broaden their general field of medical knowledge. Fifteen courses are given in the school: General medical zoology, protozoology, helminthology, entomology, tropical bacteriology, pathology, comparative pathology, tropical hygiene, a general course in tropical medicine and one in tropical dermatology, a clinical laboratory course, one upon the poisonous plants of the tropics and their effects, venomous animals, tropical climatology, and sunlight. To those successfully completing these courses in tropical medicine which are pursued for six months a diploma in tropical medicine is granted. In this connection the general medical student and investigator should bear in mind that perhaps no other training will assist him more in his understanding of modern scientific medicine or give him a wider grasp of the subject than a training in tropical medicine and its allied branches, protozoology, helminthology, entomology, and bacteriology. I say allied branches, for, as I have emphasized elsewhere, these subjects are very closely linked with and really form the groundwork of tropical medicine. They should be taught together, and better opportunities exist for the study of all of them in connection with tropical work than anywhere else. In addition, for those who wish to pursue their studies further in tropical medicine, other opportunities are offered leading to a degree in tropical medicine.

Candidates for this degree may carry on their original investigations relating to the subject of the thesis required for this degree either in laboratories situated in the United States or in various tropical or subtropical countries. I have recently been appointed Director of Laboratories and Re-

search Work of the United Fruit Company of Boston and New York, and by arrangement with this company candidates for the degree in tropical medicine, as well as a limited number of other investigators, will be offered opportunities of pursuing their studies in the various hospitals of this company in Cuba, or in Central or South America, and while performing such studies and the necessary clinical laboratory work of the hospitals, will receive their board and lodging and have their laundry work performed free of charge. I have recently visited all of these stations and hospitals and have become informed regarding the opportunities offered in the different ones for the study and investigation of tropical medicine. One cannot fail to be struck by the abundant opportunities for study and research which exist in many of these localities. In Banos and Preston in Cuba, in Guatemala, Spanish Honduras, Costa Rica, Panama, and Colombia, the United Fruit Company has already established well-equipped hospitals with laboratories attached where large clinics have been opened, and where abundant material for the study of tropical diseases may be found. At Quirigua there is situated the most satisfactory hospital in relation to construction, with the exception in some respects of the Philippine General Hospital at Manila, which I have visited in the tropics. This hospital is of steel and concrete structure, is 340 feet long, and has two connecting wings. It has accommodations for 250 patients, has wide verandas, and is thoroughly screened.

Owing to the different geographical positions and physical features of the districts in which a number of these hospitals are situated, the climatic conditions, the fauna and the flora in the vicinity of them vary greatly, and, as might be expected, a corresponding variation in the incidence and character of disease also occurs in the different stations. At Bocas del Toro and Port Limon, Costa Rica, where large hospitals of the company are situated, but 150 to 200 miles from the Canal Zone, a very different climate from that found more commonly in the tropics is encountered. In Bocas and Limon there is no distinct dry and wet season; on the contrary, it rains every month in the year, and often for weeks and sometimes for months almost continuously. It is in these localities that the banana disease prevails so extensively. This disease is said to be due to one of the fungi (*Ustilaginoidella musaperda*) which develops particularly in the wood vessels of the plant and the immediately surrounding tissues. The water supply is thus gradually cut off by the rapidly developing mycelium, and the plant dies. The damage done by the fungus, however, is apparently not only of a mechanical nature, since there are evidences of the action of an enzyme producing pathological changes in the cells of the plant. This disease is rapidly destroying the finest banana plantations in the world, situated in Costa Rica and Panama. On the other hand, in Santa Marta, Colombia, probably the oldest town in South America, it sometimes does not rain more than once or twice in a year. Here, where the banana plantations in the vicinity are irrigated by means of mountain streams, this disease does not occur. In this city another large hospital of the United



Fruit Company has just been built. A large proportion of the inhabitants are afflicted with a disease known as caraate, the etiology of which is also still not definitely determined. This is another problem which we intend to investigate in the near future.

Nowhere in the United States will the student of public health find such opportunities for study and development as in the vicinity of many of these stations, and in a number of localities near by the sanitary conditions are so bad as to be almost beyond description. With the opening of the Panama Canal, also, the western coast of South America is at our doors, so to speak, and a lucrative field for development in tropical medicine also exists there. The opportunities for medical and sanitary work in such cities as Guayaquil, Ecuador, Manaus and Iquitos in Brazil are at the present time unbounded.

One of the functions of the school of tropical medicine at Harvard, will be to send expeditions to regions in the tropics where students and assistants can carry on studies relating to the elucidation of special problems. Such an expedition was sent from the school during 1913, which, besides collecting much valuable material for study and teaching purposes, was also able to throw much light upon the diseases Oroya fever, Verruga Peruviana, and Uta. At least two other expeditions from the school, one to Central America and one to Africa, are planned for the coming year.

It is advisable that the student in tropical medicine should not only be trained in the laboratory branches I have mentioned, but he should have in addition a complete training in general clinical medicine in order to be able to recognize new clinical conditions in tropical countries. Much confusion in tropical medicine has resulted sometimes through the investigator failing to identify from a clinical standpoint an already recognized disease, and regarding it as a new condition, and *vice versa*, wrongly diagnosing an undetermined affection as an already recognized disease. For this reason

arrangements have been made by the Harvard School to establish a hospital or ward devoted to the treatment and study of tropical diseases, so that practically all cases of tropical disease reaching the port of Boston will be sent to this institution. It is also believed that many individuals that have contracted tropical diseases during their travels in hot countries will repair to this hospital for treatment, and it is hoped that other medical institutions in the United States will send patients afflicted with tropical diseases there.

Thus it will be seen that a number of important interests have already been brought together in Boston in relation to tropical medicine, and we ask your cooperation and support in the further extension of the work. As I have intimated, the development of a school of tropical medicine in this country has been slow, and the movement to put *one* upon a satisfactory and permanent basis can obviously best be aided by a concentration, and not by a division of the interests relating to this subject.

I fear that I have perhaps already expended too much of your time in the discussion of this subject, and I will close by merely calling your attention to the fact that many positions are available for American physicians well trained in tropical medicine. In addition to the opportunities furnished for the practice of medicine in the southern United States and our tropical dependencies, our various civil-government-medical-services furnish excellent opportunities in tropical and subtropical stations for physicians in hospital, public health, or laboratory work. The Rockefeller International Health Commission can also furnish a career to men properly trained in tropical medicine, and the United Fruit Company of New York and Boston, has an extensive medical service under the direction of Dr. Robert E. Swigart, and likewise offers attractive opportunities to young men. The Harvard School of Tropical Medicine also has vacancies on its staff for competent workers in this subject.

## THE CAUSES OF INDIGESTION—A STUDY OF 1000 CASES.<sup>1</sup>

By DOUGLAS VANDERHOOF, A. M., M. D.,

*Professor of Medicine in the Medical College of Virginia, Richmond, Va.*

This clinical study is based on the histories of 1000 consecutive patients who presented themselves for the relief of chronic or recurring indigestion. The series is made up entirely of private cases, for the most part referred by the attending physicians. It embraces only those patients whose chief complaint was attributed to some disturbance of digestion, such as "stomach trouble," dyspepsia, abdominal pain or distress, flatulence, vomiting, etc., and entirely excludes patients complaining of other symptoms who were found, on examination, to have some intra-abdominal lesion.

The classification of the causes of indigestion has always

been a matter of some difficulty in the past and, as a result, a purely symptomatic nomenclature has obtained which still appears in most text-books on the subject. The recent advances in physiology and surgical pathology, however, together with the intrepid explorations of our surgical colleagues, have accomplished many steps in the problem of assigning the various symptoms of maldigestion to their proper causes.

Now that the real nature of stomach symptoms is being more definitely understood, the difficulty of attempting a classification of stomach affections becomes apparent. As James Mackenzie has well said, we have been attempting to differentiate what cannot be differentiated.<sup>2</sup> He emphasizes

<sup>1</sup> A clinical lecture delivered in Baltimore, October 6, 1914, on the occasion of the twenty-fifth anniversary of the opening of The Johns Hopkins Hospital.

<sup>2</sup> J. Mackenzie: "Symptoms and Their Interpretation." 2d edition. Chapter XII.



the fact that, except for certain characteristic conditions which refer only to a very small proportion of the cases, all the symptoms are of a reflex nature, pain, cutaneous and muscular hyperalgesia, muscular contraction, vomiting, air-swallowing, etc. As any adequate stimulus may suffice to produce these symptoms, and as this adequate stimulus may arise from the most varied causes, it follows that there is a great similarity of symptoms in diseases of the most varied kinds.

Mackenzie and others have shown that in visceral disease certain areas in the spinal cord become so irritable that stimuli from the periphery give rise to an exaggerated response. "This irritable focus in the cord is of great frequency in stomach affections. When pain occurs after food it must not be assumed that there is an inflammation of the mucous membrane, or that the stomach itself is hypersensitive. The ingestion of food under normal circumstances is accompanied by reflex processes which are not perceived, and pain merely indicates that there is an irritable focus in the cord through which these reflex processes pass. The lesion inducing the irritable focus in the cord may not necessarily be a stomach lesion at all, but may arise from a neighboring organ whose reflex center in the spinal cord is in close proximity to that of the stomach." Thus in gall-stone colic, or in acute inflammation of the appendix, the pain may be so violent as to invade the stomach area in the cord, and in chronic inflammations of these same organs this invasion of the area in the cord gives rise to the various trains of symptoms referred so constantly to the stomach.

In order to determine the proportionate frequency of the various causes of indigestion, I have tabulated the clinical diagnosis in a series of 1000 patients examined by Dr.

TABLE I.  
CAUSES OF INDIGESTION. SUMMARY OF 1000 CASES.

	Per cent.
Appendicitis.....	24.6
Cholecystitis.....	11.7
Neurosis.....	10.1
Peptic Ulcer.....	9.4
Chronic Gastritis (Achy- lia Gastrica).....	3.6
Visceroptosis.....	3.4
Cancer, stomach.....	2.3
Post-operative Adhesions	1.6
Enterospasm.....	1.5
Migraine.....	1.3
Cancer, intestines.....	1.2
Infectious Diseases.....	0.8
Enterogenous Toxemia..	0.5
Affections of—	
Kidneys.....	7.1
Lungs.....	2.8
Heart.....	2.3
Eyes.....	2.0
Female Pelvic Organs	1.9
Blood and Ductless Glands.....	1.8
Liver.....	1.1
Nervous System.....	1.1
Ears.....	0.8
Miscellaneous.....	5.8
Diagnosis not made.....	1.3

Hutcheson and myself. (Table I.) Each patient has received thorough study, including a careful history, complete physical examination and the necessary laboratory analyses, including as a routine one or more gastric analyses, urine

examination, and differential blood count with hemoglobin determination. Advantage has been taken of skillful X-ray studies, and most helpful have been the free and unconstrained consultations with my surgical confrères, Dr. George Ben Johnston and Dr. A. M. Willis, in whose operating rooms I have seen many of these patients treated surgically.

A summary of Table I is contained in Table II. This shows that appendicitis and cholecystitis are responsible for approximately 35 per cent of the cases of chronic or recurring indigestion; peptic ulcer and neuroses, each 10 per cent, and carcinoma involving the stomach or bowels, 5 per cent. Ten per cent of the cases fall into a group including chronic

TABLE II.  
SUMMARY OF TABLE I WITH APPROXIMATE PERCENTAGES.

	Per cent.
Appendicitis and Cholecystitis .....	35
Peptic Ulcer .....	10
Neuroses .....	10
Cancer (Stomach and Intestines) .....	5
Chronic Gastritis, Visceroptosis, Peritoneal Adhesions, Entero- spasm and Enterogenous Toxemia.....	10
Affections of Kidneys, Lungs, Heart, Eyes, Blood and Ductless Glands, Ears, Central Nervous System, Female Pelvic Organs; Migraine and Chronic Infectious Diseases .....	25
Miscellaneous Conditions .....	5
	100

gastritis, visceroptosis, peritoneal adhesions, enterospasm and enterogenous toxemia; while 25 per cent are included in a group in which the indigestion is a reflex disturbance from affections of the kidneys, lungs, heart, eyes, blood and ductless glands, ears, central nervous system, female pelvic organs, and migraine and chronic infectious diseases. The remaining 5 per cent, classified as miscellaneous, include such conditions as pellagra (eight cases); amebic dysentery (six cases), malaria (five cases), diseased tonsils and cyclic vomiting (in children, respectively six and five cases), intestinal parasites (four cases), together with instances of diverticulitis, peritoneal tuberculosis, cancer of the pancreas and esophagus, retroperitoneal sarcoma, etc. In those patients in whom more than one lesion existed as a possible reflex cause of indigestion, I have tabulated, according to my discretion, the one most likely to be responsible. The occurrence of both appendicitis and cholecystitis in the same patient is so frequent, however, that the figures are more correct if these two conditions be combined as in Table II.

It is very likely that the percentages attributed to peptic ulcer and to the neuroses (each 10 per cent) are too high. Many of the ulcer cases were treated medically, and a diagnosis of neurosis is often accompanied with a question mark. It is my belief that certain of these cases, if they could have been followed further, would have proved to be instances of diseased appendices or gall-bladders, and that the true incidence of appendicitis and cholecystitis approaches 40 per cent in the causation of chronic or recurring indigestion.

Of the patients in whom the diagnosis of appendicitis or cholecystitis was made, I have on the histories the record of



all who were operated on to my knowledge. In certain instances the patients refused the advice of surgical treatment, while others could not be followed. I have the operative notes of 145 of the 246 cases of appendicitis, and of 60 of the 117 cases of cholecystitis. All of these patients have been communicated with by letter in the effort to learn the end results of the treatment outlined. The replies have been subjected to a strict interpretation as to whether the patient is entirely well, much improved, or unimproved in health. In Table III is contained the result of this inquiry, which shows that of a total of 363 cases of appendicitis and cholecystitis, 205 were operated on; that of these, replies were received from 134. From these letters it is learned that 61 per cent are well, 28 per cent are much improved, and 11 per cent are not improved.

TABLE III.

RESULTS OF SURGICAL TREATMENT IN THE CASES OF APPENDICITIS AND CHOLECYSTITIS.

	Patients operated.	Patients reporting.	Well.	Much improved.	Not improved.
Appendicitis . . . .	145	93	54, or 58%	27, or 29%	12, or 13%
Cholecystitis . . . .	60	41	28, or 68%	10, or 25%	3, or 7%
Totals . . . . .	205	134	82, or 61%	37, or 28%	15, or 11%

In the effort to determine the cause of failure in 12 cases of appendicitis and three cases of cholecystitis, I have reviewed these cases in detail, but append only the following abstracts. In each case the patient's convalescence in the hospital was uncomplicated. Only one patient in the series died as the result of the operation. This was a case of gall-stones in a morphine habitué who also had chronic nephritis, and death occurred 48 hours after operation, due to suppression of the urine.

## APPENDICITIS.

CASE I (1910).—Male, age 35. Apparently a plain case with history of abdominal cramps followed by shifting of pain to lower right abdomen. No operative note except that a diseased appendix was removed through a McBurney incision.

CASE II (2061).—Female, age 40. The condition was complicated by a chronic gastritis (achylia). Operative note: "Right rectus incision. The appendix was found much diseased and adherent to the cecum. The stomach and gall-bladder were examined and found negative."

CASE III (2300).—Male, age 36. This patient's condition was complicated by evidences of hypothyroidism. His operation was preceded by X-ray examinations of the kidneys and ureters, and also a bismuth examination of the gastro-intestinal tract. Operative note: "McBurney incision. The appendix was quite large, subacutely inflamed and contained many concretions."

CASE IV (3074).—Male, age 40. This unfortunate man was most neurotic, gave a history of indigestion extending over 20 years, which had incapacitated him from work. In addition to evidences of appendicitis, he had many vasomotor symptoms. Operative note: "Right rectus incision. Badly diseased appendix adherent to the bowel. Gall-bladder and stomach negative."

CASE V (3132).—Female, age 51. Prior to operation in this case, a diagnosis of cholecystitis was made and in August, 1914 (two years after operation), she writes that she has had two acute attacks of "liver colic." Operative note: "I operated through a right rectus incision. There were no stones in the gall-bladder but she had chronic cholecystitis, a hard enlarged pancreas, and an inflamed and adherent appendix. I drained the gall-bladder and removed the appendix."

CASE VI (3134).—Female, age 43. At the time of operation, 18 months ago, this patient had evidence of marked visceroptosis and increased blood-pressure, together with a fibroid uterus. She recovered promptly from her operation but writes that she is not at all well, has had attacks of impaction of the bowels, suffers much from flatulence and has not gained in weight or strength. Operative note: "I opened the abdomen in the middle line, finding chronic appendicitis and multiple fibroid growths of the uterus. I amputated the appendix and did a supravaginal hysterectomy. I palpated the gall-bladder and found it normal."

CASE VII (3532).—Female, age 37. This patient gave a history of indigestion "since girlhood," punctuated with typical attacks of acute appendicitis, beginning with epigastric cramps, pain radiating down to lower part of abdomen, with nausea, and requiring morphine. Eighteen months after operation she writes that she suffers from nausea, acid stomach, distress after meals and marked flatulence. Operative note: "Operation showed chronic appendicitis with post-cecal Lane's kink. The uterus showed small intramural fibroids. The stomach and gall-bladder were found negative. Appendectomy, abdominal hysterectomy and perineorrhaphy."

CASE VIII (4008).—Female, age 52. This case was complicated with chronic fibroid phthisis and marked visceroptosis. Fourteen months after operation she writes that she has frequent attacks of epigastric pain and much flatulence. Operative note: "I operated through a right rectus incision, removing a subacutely inflamed appendix and draining a chronically inflamed gall-bladder."

CASE IX (4241).—Female, age 44. This patient was operated on for peptic ulcer, having given a clear history, including coffee-ground vomit and passage of tarry stools. Operative note: "Right rectus incision. The stomach was carefully examined as was also the duodenum and no ulcer could be found. The gall-bladder was also negative except for a slight adhesion between it and the duodenum. The appendix showed some evidence of inflammation and was removed."

CASE X (4283).—Female, age 23. This patient gave a typical account of appendiceal indigestion dating back six years, with a history of epigastric cramps of gradual onset followed by much soreness, and requiring hypodermic of morphine. There is no operative note but she writes that she was operated on at her home and her appendix removed, but she has derived no benefit from the operation and feels satisfied that she did not have appendicitis.

CASE XI (4325).—Male, age 27. This patient was operated on shortly after a second attack of acute appendicitis, when he showed tenderness and muscle rigidity in the lower right quadrant. He gave a history of indigestion of several years' duration. X-ray of the kidneys and ureters was negative. No operative note except that patient was operated on through a McBurney incision and a diseased appendix removed.

## CHOLECYSTITIS.

CASE I (2408).—Male, age 54. Operative note: "The gall-bladder was found to be much thickened and contracted, contained glairy mucus and 4 gall-stones, the largest of which measured 1 cm. in diameter."

CASE II (3054).—Female, age 39. This patient had been a great sufferer from indurative headache, was nervous and suffered from much depression at the time of her menstrual periods. Previous X-ray of the kidneys and ureters negative. Operative note not obtained except that the gall-bladder was drained and the appendix removed. Stomach, duodenum and pelvic organs found normal.

CASE III (4035).—Female, age 42. Thirteen months after operation this patient writes that she still has attacks of intense cramps in the stomach with vomiting; also suffers with sour stomach and flatulence. Operative note: "Right rectus incision. Twenty-one gall-stones removed and gall-bladder drained. Diseased appendix removed."



UROLOGY.

THE SIGNIFICANCE OF THE DISTRIBUTION OF UREA IN THE BODY.

By D. M. DAVIS, M. D.

Until E. K. Marshall, Jr., introduced the urease method of determining urea, which is just as accurate in body fluids and tissues as in urine, our knowledge concerning the distribution of urea in the body in varying conditions was limited and undependable.

The method consists in the decomposition of urea by a specific ferment obtained from the soy bean, with subsequent estimation of the ammonium carbonate formed. This decomposition is not affected by any substance ordinarily present in the tissues and body fluids.

With the aid of this method, the amount of urea in the tissues of dogs and human beings has been determined.<sup>1</sup> I shall briefly recapitulate the results of these determinations.

Table I represents the findings in two supposedly normal dogs. It will be seen that urea is present in every organ, and that the figures run very close for most organs. The fatty tissue contains very little urea—urea is not soluble in fat. The kidney and bladder show high figures—they contain certain amounts of urine, in which the urea is roughly 50 times as concentrated as in the blood. In brief, the urea content of all tissues, with these exceptions, is *the same*.

TABLE 1.

Tissue or fluid.	Mg. urea in 100 gm. tissue or 100 cc. fluid.		Tissue or fluid.	Mg. urea in 100 gm. tissue or 100 cc. fluid.	
	D 13.	D 12.		D 13.	D 12.
Blood.....	{ 28 27	..	Intestinal.....	30	24
Blood serum.....	{ 29 29	22	Mucosa.....	29	21
Bile.....	32	21	Parotids.....	29	37
C-S fluid.....	25	21	Thyroid.....	30	6
Liver.....	{ 32 23	25	Omentum.....	{ 5 5	23
Muscle.....	{ 25 25	18	Lymph glands..	..	17
Heart.....	{ 28 30	22	Eye.....	..	17
Brain.....	{ 28 28	20	Spinal cord....	..	21
Lung.....	{ 31 33	22	Testicles.....	{ 30 32	52
Spleen.....	{ 28 29	20	Prostate and urethra.....	..	164
Pancreas.....	{ 26 25	18	Bladder.....	..	221
			Kidney.....	{ 183 159	...
			Urine.....	1640	

Table 2 represents the findings in a dog where 20 gm. of urea were injected intravenously. In the first column are figures obtained from tissues removed before the injection, in the second four hours after the injection, at which time the animal was sacrificed. The urea has distributed itself fairly uniformly to all parts.

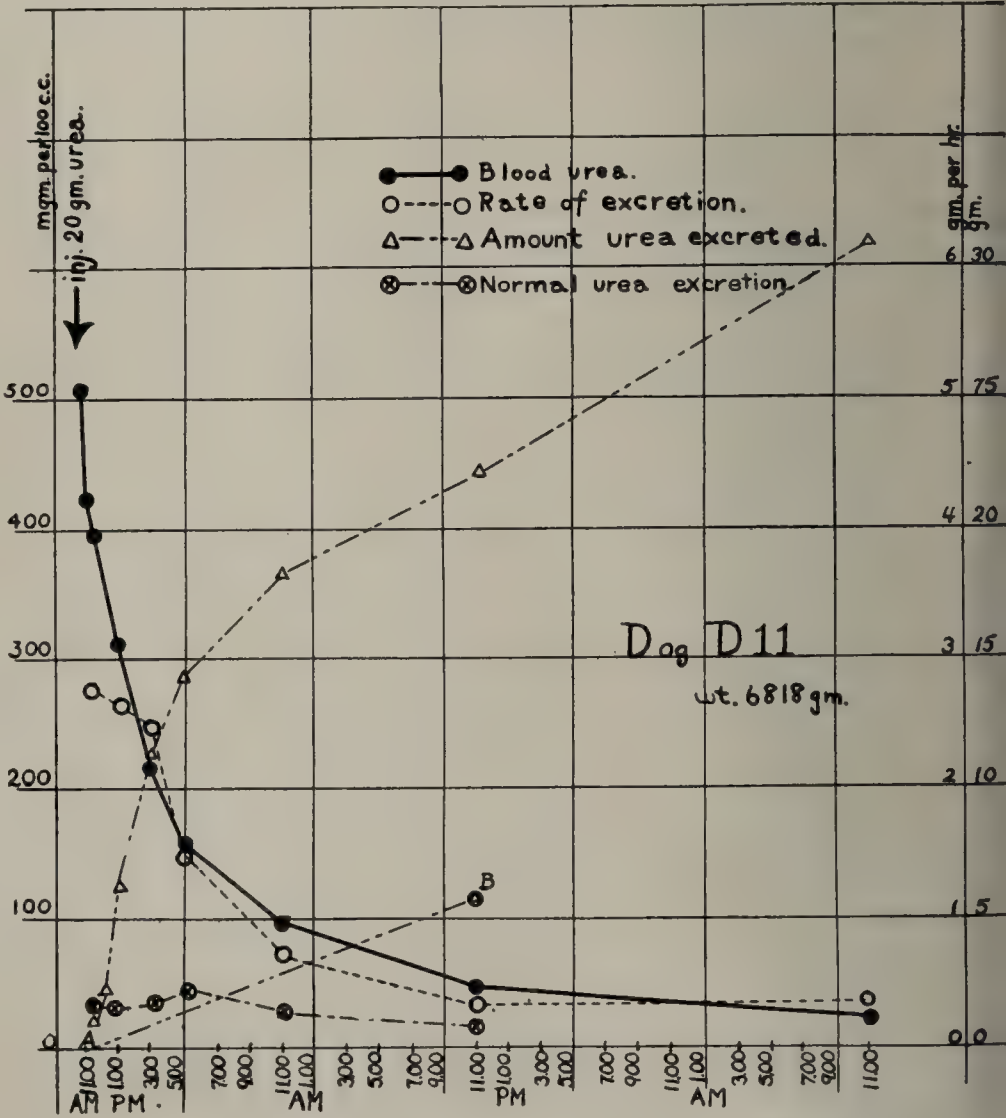
TABLE 2.

Tissue.	D 4.	
	Mg. urea per 100 gm. tissue before injection.	Mg. urea per 100 gm. tissue at death.
Blood serum.....	21	493
Liver.....	22	354
Muscle.....	24	377
Spleen.....	..	409
Heart.....	..	367
Brain.....	..	397

TABLE 3.

Tissue or fluid.	D 10.	
	Mg. urea per 100 gm. (cc.)	
Blood serum.....	827 (780)	
Bile.....	788	
Liver.....	762	
Pancreas.....	750	
Muscle.....	768	
Kidney.....	963	

TABLE 4.



Reproduced from the *Journal of Biological Chemistry*, 1914, XVIII, 71.

<sup>1</sup> Marshall and Davis: Jour. Biol. Chem., 1914, XVIII, 53.



Table 3 shows the distribution in a dog with both ureters tied (48 hours).

Table 4 represents the excretion of urea after intravenous injection of 20 gm. in a healthy animal (dog). The black line gives the blood urea figures at intervals after the injection. The interrupted line gives the rate of excretion, calculated from the urinary findings, in grams per hour. The blood urea falls more rapidly at first—it is still being distributed to the tissues. The rate of excretion falls less rapidly at first; the kidneys are presumably doing somewhere near their best. Later the two lines practically coincide. As they near normal levels, the excretion is less rapid, and the approach to normal is very gradual indeed.

It has been found by other experiments that the excretion of urea may be hastened by giving large quantities of water, since the concentration of the urine in urea never rises above a certain point. Ordinarily the excretion of urea is higher during the day, when food is taken, than during the night.

The normal blood urea figure for human beings is near 30 mg. per 100 cc. or gm. In some autopsy specimens, 650-700 mg. per 100 gm. have been found. This represents in the neighborhood of 500 gm. urea for the whole body: at 30 gm. per day, the usual figure given for formation of urea, it would be the entire product of the body for over two weeks. Since the urea content often rises very rapidly, especially in the terminal stages, we may have to deal with changes in the rate of production of urea by the body.

At any rate, we have the explanation of the slow rise of the blood urea in ordinary nephritis, when the urine urea is low. The substance is spread over the entire body, so to speak, in a uniform layer. Its presence in high concentrations does comparatively little harm. It does not cause hemolysis in any concentration. To kill dogs, about 1 per cent of the body weight must be introduced. It seems beyond doubt that other factors must cooperate with urea in producing death in nephritis.

In studying cases of nephritis, it is found that urea retention is very common. With rapidly advancing disease, the blood urea rises constantly. When improvement occurs, it is regularly indicated by a fall in the blood urea towards normal. In other cases, however, it is found that the blood urea is markedly above normal, but that it remains constant. The fact that urea is a powerful diuretic may cast some light on this condition. The increased amount present in the blood would stimulate the injured kidneys until they were able to throw off an amount equal to the daily production. Such a mechanism would tend to maintain automatically the same level of urea concentration in the blood. We know further that if in such a case a diet very low in protein is instituted, with a consequent drop in the daily formation of urea, the blood urea will fall to a lower level.

In attempting to utilize this diuretic action of urea, one should proceed with great caution, since Herter has shown that kidneys damaged by cantharadin fail to respond with diuresis to the introduction of urea.

It is evident to everyone that there are innumerable kinds of nephritis, in each of which the excretion of different substances is affected differently. This fact handicaps us in our efforts to interpret the significance of the urea content of the blood in any case. The excretion of urea may be comparatively unaffected, while other substances are retained. The excretion of urea may depend to a considerable extent on the excretory conditions for other substances, as water. The formation of urea depends directly upon the diet, and, as I have indicated above, may vary also with other conditions with which we are as yet comparatively unfamiliar.

Therefore, the quantity of urea in the blood of a patient at any moment can naturally give us much less information than a study extending over some time, and including as many factors as possible; *i. e.*, blood determinations, urine determinations, diet, and other methods of estimating renal function.

## RENAL FUNCTIONAL TESTS.

By JOHN T. GERAGHTY, M. D., Baltimore, Md.

In recent years, there has been a rapid advance in the methods of estimating the functional capacity of organs in health and disease, and the methods for estimating the renal function have probably developed to a higher degree than methods for estimating the function of any other organ. It is now recognized in diseases of organs that it is not so much the variation in the anatomical structure, which is important, but rather the reduction in the power of the organ to functionate properly. While in the average case the reduction in functional power is roughly proportionate to the degree of anatomical change, it is well known that gross anatomical changes may be present in the kidney with comparatively little disturbance of function, while, on the other hand, the most profound functional derangement may be present when the visible anatomical variations are extremely slight. A striking

example of extreme reduction in functional power with very slight anatomical changes recently came under observation:

This was a man, 55 years of age, who had been in comparatively good health up to six weeks before he was first seen. Following excessive physical labor, he was suddenly seized with nausea and vomiting and three days later a slight hematuria was noted. Examination showed a well-nourished man; mental condition bright; pulse and temperature normal; leucocytes normal. Blood pressure 150 mm. The urine was a light wine-color and a heavy cloud of albumin was present upon heating, which could readily be accounted for by the amount of blood present. Careful microscopic study showed very few casts. On cystoscopic examination the blood was seen to be coming from both kidneys. The true nature of the condition was not suspected until estimations of renal function were made. No phthalein was excreted in a period of three hours and an estimation of the blood urea showed  $2\frac{1}{2}$  grams to the liter, a very high concentration. Patient died in uremia one



week later and examination of the kidneys showed a most interesting condition.

On gross examination, the kidneys were about normal in size and the cut surface showed very few changes. Microscopic study showed a slight adhesive glomerulitis with complete hyalinization of occasional glomeruli. The tubular cells were apparently entirely normal, but there was a marked increase in the connective tissue between the tubules. The histological picture was that of a mild grade of chronic, diffuse nephritis. Although this patient died of renal insufficiency, the histological structure of the kidney gave very little information of the profound functional disturbance which was present. It should be remembered that even our finest histological methods are gross, and, as this case illustrates, may not reveal the severe chemical disturbance which is present in the renal cell.

The number of functional renal tests is now so large that it is impossible to use all of them in any individual case. It is not necessary, moreover, since all of the available information is forthcoming at times from a single test, or from the proper combination of a small number of tests. Only through familiarity with the reliability, value, limitations and significance of the findings of each test in various types of disease is the most profitable selection of tests made possible.

Certain tests, such as lactose and the chlorides, prove of great value to the internist but are practically valueless from the standpoint of the surgeon. Some tests are valuable for the estimation of total function, but cannot be used in conjunction with ureteral catheterization. Other tests may be of no value for the estimation of total function but may be very valuable in conjunction with ureteral catheterization for estimating the relative functional ability. For instance, urea estimations of the 24 hour output, give, as a rule, information of but little value, but urea estimations of catheterized specimens give a very accurate idea of the relative amount of work done by each kidney.

The renal functional capacity is usually ascertained in one or two ways. First, tests of excretory capacity from the quantitative determination of the excretion of various substances in the urine; second, tests of retention through the determination of the concentration of certain substances in the blood cryoscopy, blood urea and total nitrogen being the tests most generally employed. The information given by many of the tests is of the same character, but is more accurately furnished by one test than by others. For example, there is a certain parallelism between the excretion of the different dye substances, but as phthalein furnishes more accurately all the information obtainable from this group of substances, no advantage attaches to the employment of all.

Studies of renal function in medical cases fall into two great groups: First, those attempting to differentiate between tubular and glomerular involvement and those attempting to determine total function. Glomerular function, according to Schlayer, is indicated by the excretion of water and lactose and that of the tubules by salt and potassium iodid. Lactose and potassium iodid, both being substances foreign to the body and hence not so easily influenced by extra-renal factors, have been considered to be more reliable indices than salt. Schlayer and his co-workers, from their studies with lactose, water, salt

and iodid tests, have attempted to divide nephritis from a purely functional point of view into four groups: purely vascular, vasculo-tubular, tubulo-vascular and purely tubular. The evidence to be found in the literature for the assumption that lactose is chiefly excreted through the glomeruli is not convincing and experiments carried out on the frog's kidney have demonstrated beyond doubt that the tubules are capable of excreting lactose. Our studies have led us to the conclusion that the potassium iodid test, as used by Schlayer and in which he has placed greatest confidence for indicating tubular functional capacity, is unreliable. We have not encountered any cases of pure tubular nephritis. When both systems are involved, we do not feel that the test can determine whether the tubular or vascular injury is preponderant. Mild, passive congestion alone in many instances produces the same functional picture which Schlayer describes as characteristic of vascular nephritis. Consequently a combined functional and clinical study is essential in order to differentiate two functionally similar but clinically different conditions. At present so little is positively known or proved concerning the specific function of any individual part of the kidney, that any attempt of the kind mentioned to classify nephritis as above mentioned is premature.

All of the information furnished by the lactose test can be obtained more simply and reliably by the phenolsulphonaphthalein test. It has, however, one peculiar field of usefulness; namely, in the very mild types of nephritis occasionally encountered, in which difficulty arises in deciding as to whether the condition is really a mild nephritis or a functional albuminuria. In this type of mild nephritis, the phenolsulphonaphthalein excretion may be normal, the tests of retention are negative, but the lactose will show a delayed excretion. The lactose test may be accepted as an index of vascular disturbance, but a decreased lactose does not necessarily mean a glomerular nephritis.

In all cases of severe nephritis, or in cases in which the phthalein excretion is very low, one of the tests of retention should be employed, either the total incoagulable nitrogen or an estimation of the blood urea. The methods of estimating blood urea have now been developed so that they do not require expensive and elaborate apparatus, nor long chemical training. The urease method of Marshall we have found very accurate and simple. Folin and Dennis have shown that normally there is present in the blood about 300 mg. of urea per liter. When bilateral renal disease is present a retention of urea occurs, the degree of urea retention increasing as the excretory ability of the kidney decreases. In occasional instances, the urea retention may reach the astonishing degree of 7 grams per liter. Such a urea retention, is, however, very rare. In the average case, even with marked renal insufficiency, the blood urea seldom rises above 2 to 3 grams. A blood urea of less than .6 gram per liter is of little prognostic significance. It has been found that there is an exceptional type of nephritis showing oedema, albumin and casts, in which the general function is normal except for salt. Indeed, a hyper-permeability may exist for other substances, the salt alone



being delayed in its excretion. However, in the vast majority of cases, all the information obtainable from functional tests will be furnished by phenolsulphonephthalein. Where the excretion of phthalein is markedly reduced, an estimation of blood urea is usually performed. By means of these functional tests, together with clinical studies, it is possible to obtain a much clearer conception of the renal condition than from clinical studies alone.

Renal functional tests have already proved their great value to the surgeon in two types of cases: First, in the surgical diseases of the kidney secondary to obstruction of the lower urinary tract; and, secondly, in the unilateral and bilateral surgical diseases, in association with ureteral catheterization. In previous communications on the subject of renal function, attention has been called to the value of phthalein in affording an index to the renal functional capacity in the changes resulting from obstruction in the lower urinary tract. It was pointed out that such patients are frequently the subject of hydronephrosis, pyelonephrosis, pyelonephritis, pressure atrophy and the resulting changes in functional activity, and that the urine output, urea and total solids might be practically normal and yet the patient be on the verge of renal failure, which would surely be precipitated by any radical surgical interference. The phthalein test was shown to be of value in all these cases and to allow of differentiation between those with severe renal damage and those in which the renal involvement was slight. It was further shown that a marked improvement of the renal condition and the decreased operative risk which followed the adoption of preliminary treatment, either from the use of an inlying catheter or suprapubic drainage was the result, to a large extent, of the improvement of the renal functional capacity. It was held that the test made it possible to determine the cases suitable or unsuitable for operation and also to determine in any given case the most propitious time for surgical intervention.

#### FUNCTIONAL TESTS IN ASSOCIATION WITH URETERAL CATHETERIZATION.

In this group it is desirable to have information in regard to three phenomena: First, the total or combined renal function without ureteral catheterization; second, the relative function; and third, the absolute functional value, if possible, of each kidney. Functional tests in the past have demonstrated their great value in this group, but they have at most been able to determine only the relative working capacity of each kidney and have shed very little light on the absolute functional capacity of each organ, or on the total or combined renal function. In this class of cases, the shortcomings of most of the functional tests are very evident, since they give us only the relative functional value of the kidneys. One kidney may be doing two or three times as much work as the opposite organ, yet be incapable of assuming additional work or of carrying on adequate work when needed. Phthalein has prognostically shown great advantage over these other tests in that it indicates the absolute as well as the relative value of each kidney, so that one knows not only which is the diseased

or more diseased but the amount of work which each is doing relative to the other, and what is yet of greater importance, the amount of work of each relative to the normal, since this allows a prognosis concerning the capacity of the remaining kidney to carry on renal function. The phthalein test is incomparable so far as total function is concerned and gives us information frequently unavailable from any other source. In cases in which leakage and inhibition are absent, it furnishes in itself all the necessary information in regard to the function of each kidney. The employment of functional tests in association with ureteral catheterization is attended with two great difficulties, which, in certain cases, make it impossible always to obtain all the desirable information from any one test; namely, inhibition of function and leakage around the ureteral catheter. It is the occurrence of these two difficulties, but particularly inhibition, which renders experience and judgment necessary for the interpretation of functional findings in association with ureteral catheterization. Any discrepancy due to inhibition can be detected readily from the determination of phthalein of total renal function without ureteral catheterization. For instance, with the total phthalein excretion normal, or nearly normal, one kidney at least is normal or practically so. If on ureteral catheterization one should find on one side decreased function and pathological findings which under ordinary conditions would be an indication for nephrectomy, one should not hesitate to remove the diseased kidney even though the function of the supposed healthy kidney, estimated with the aid of a catheter, showed an apparently dangerously low excretion. The low function here is clearly the result of inhibition, the extent of which is indicated by the discrepancy of the separate function and the total function without ureteral catheterization.

While it is true that in the vast majority of cases a successful nephrectomy of the diseased side from the standpoint of renal function can be performed where the urine from the opposite kidney is found apparently normal on microscopic and chemical analysis, unfortunately, however, the problems are not always so simple. Cases of bilateral disease are encountered in which a knowledge of the renal function becomes of absolutely vital importance and in which every source of information must be called upon before the proper line of procedure can be employed. Again, in certain cases it may be possible to introduce the catheter only on one side and in such cases one must depend to a great extent upon the information derived from function as to the condition of the opposite kidney. The recognition of hypoplastic and infantile kidneys is practically impossible without functional estimations. This infantile kidney, while rare, is a particularly dangerous type, because the urine which is secreted by this kidney is apparently normal in every respect, except that of quantity. Functional estimations have proved also of great value in the differentiation of pyelitis and pyelonephritis. In pyelitis, the renal function is practically normal, while in pyelonephritis there is decreased function, depending upon the degree of obstruction. It has enabled us to select with considerable accuracy cases of renal infection suitable for pelvic lavage.



## LIMITATIONS OF FUNCTIONAL TESTS.

Functional studies reveal only the excretory capacity of the kidney. By themselves they do not make the diagnosis or settle the prognosis. The value of any of these excretory tests is purely empirical, because of lack of sound physiological information dealing with the ultimate physics and chemistry of the excretion of any substance by any part of the kidney, the tubules or glomeruli. They indicate only the functional value of the kidney at the time at which the test is performed, but cannot of themselves indicate what the renal function will be to-morrow or next week. This latter information is to be derived from the knowledge of the underlying pathological process which is producing the reduced function. For

example, a degree of renal function in chronic nephritis which would indicate a very grave prognosis might in polycystic kidneys be consistent with a considerable period of life. Again, there is a kidney whose function is being markedly reduced by the presence of a stone, blocking the ureter or in the pelvis. It is impossible to say, from functional studies alone, of what power of regeneration that kidney is capable after the removal of the cause of the reduced function.

Notwithstanding that functional tests have their limitations, if they are used in association with careful clinical studies and a proper regard for the information which they can furnish, a clearer conception of the renal condition will be obtained than from clinical studies alone. It will, in many instances, enable us to adopt a more intelligent line of treatment.

THE PREPARATORY TREATMENT OF UROLOGICAL OPERATIONS.<sup>1</sup>

By FRANK HINMAN, M. D.,

*Resident Genito-Urinary Surgeon, The Johns Hopkins Hospital.*

Surgical risks may be considered as both operative and clinical. The important operative circumstances that influence the recovery of the patient are the surgical sense and technique of the operator, the character and extent of the operation, the operative complications, the choice and nature of the anesthetic, and the resultant degree of operative shock. Of clinical conditions, the mental and physical state of the patient, his bodily resistance, and his power of reaction to operative and post-operative complications, determine the outcome. For most operations, perhaps for all, the first group of circumstances is the more important. Nevertheless, the surgeon, who neglects the careful consideration of clinical risks, proper preparatory treatment and the selection of a favorable time for operation, fails to reduce his mortality to the minimum.

In urological surgery the group of clinical conditions attains equal importance with the operative. This is due to the fact that a majority of urological cases have urinary involvement, of one kind or another, with resultant danger to or loss of renal function; and, also, to the frequency of urological conditions in old men whose resistance, frequently, has already been reduced by renal or cardiac burdens.

These clinical risks do not, as a rule, occur singly, but are more often associated with each other, with relative degrees of importance, one or more, possibly, being secondary to the primary clinical disturbance; and in their correct estimation a familiarity with many clinical and laboratory methods of examination is demanded. After the diagnosis and the clinical condition of the case have been determined by these means, the question arises, is the case a safe operative risk? And if not, what special line of preparatory treatment should be instituted in order to make it a safe risk? To meet this question this clinic has adopted certain routine and special

methods of study and treatment in order to wisely estimate the surgical risk, to institute preparatory treatment intelligently, and to select the most favorable time for operation.

Urological operative risks may be clinically grouped under five headings: (1) renal, (2) cardiac, (3) cardio-renal, (4) hypertension, and (5) infections. Each group may be again subdivided: the renal into chronic nephritis, uremia, renal injury from back pressure due to enlarged prostate, stricture, etc.; and surgical kidney, unilateral and bilateral, as tubercular, polycystic kidney, renal calculus, etc.; the cardiac, into endocardial, myocardial disease, and cardiac involvement with or without chronic passive congestion of the kidneys; the cardio-renal, into combinations of the above conditions; hypertension, into the many different conditions causing it; infection, to include septic kidney and acute nephritis, pyelonephritis, pyelitis, cystitis, epididymitis, prostatitis, etc., and infectious diseases, as bronchitis, pneumonia, etc. There are also other clinical risks such as anemia, diabetes, etc.

In determining these various clinical associations, the routine history and physical examination are of first importance. This early study indicates special lines of investigation that will probably prove most fruitful, and eliminates others as needless in estimating the true clinical condition. A careful determination of the chemical and microscopical constituents of the urine is demanded in every case, no matter what the genito-urinary diagnosis may be; and is, of course, included in the routine physical examination; and specimens of urine are collected for examination every day during the treatment preliminary to operation. A blood-pressure estimation and a phthalein test are also considered to be an essential part of the routine physical examination. A case found to be negative after the above examinations, with a good history, sound organs, normal urine and satisfactory blood-pressure and phthalein test is considered an excellent clinical risk—a risk in which clinical conditions will not add to the operative dan-

<sup>1</sup> Read October 7, 1914, at the exercises of the Twenty-Fifth Anniversary of The Johns Hopkins Hospital.



gers. In case the above routine examination reveals abnormalities in any part, lines of special study are then followed by which their character and extent may be known, and with this study, as indicated by it, are combined routine and special methods of preparatory treatment. If the heart is found to be the cause of the symptoms, daily blood-pressure readings and repeated physical examinations are made, and electrocardiogram records are taken as a control of treatment. Where the kidneys are indicated as responsible, regular urinary studies are undertaken, of which repeated phthalein tests are the most important, it being the routine procedure to make regular bi-weekly observations upon all cases. Where the phthalein is low the amount of blood urea or blood nitrogen is determined, and where nitrogen retention is present, these estimations are made every week at least, sometimes oftener. The fluid intake and the urine output for each 24 hours is carefully measured. The presence of chloride retention or renal acidosis is determined in special cases. In many cases of renal involvement, even with a very low phthalein output, the urea, chlorides and acids of the blood will be found to be normal, so that a repetition of these tests will not be necessary, reliance being placed upon the phthalein test alone, for the control of treatment and the selection of a favorable operative period. A static phthalein, that is, a phthalein output which upon repetition remains practically unchanged, is the state to be particularly sought for. Where the function of the kidney is gradually improving or failing, the latter obviously, an operation is not as safe as when it is stationary. No percentage limit can be fixed below which an operation is contra-indicated. It is the picture of repeated tests that counts.

The preparation of chronic nephritis for operation necessarily varies with the character and extent of the disease. Forced feeding of water is invaluable in most cases, but it must be carefully controlled, particularly in cases with cumulative phenomena, as shown by the fluid and urine chart and the nitrogen and chloride tests. Where nausea or vomiting is present the necessary water should be given per rectum or by infusion. Free catharsis is extremely important in these cases and the average of each individual cannot be too carefully watched. A daily bowel movement is essential. The regular daily ingestion of a mild laxative is preferable to an irregular strong purge following a series of ciphers. When edema is present the regulation of the salt intake, or even a salt-free diet for a time is indicated. Where there is retention of nitrogen, the regulation of the meat ingested and often a complete non-protein diet, are indicated. In the presence of an acidosis, soda bicarbonate, in massive doses, will often give most gratifying results. The alkali may be given by mouth, by rectal feedings or by infusion, and should be vigorously pushed until the urine becomes alkaline and then continued in smaller amounts. The giving of lactose or glucose is very advantageously combined with it and supplies a harmless and often much needed food. Sweat baths, and in certain cases bleeding by venous puncture, are of distinct assistance. The practical application of Abel, Rowntree, and Turner's method of plasmaphæresis (plasma removal with return of corpuscles) in these cases offers brilliant possibilities. The

extreme importance of the above brief outline is indicated by the fact that several old men (recently admitted to the hospital in pronounced uremia, persistent vomiting, delirium, and convulsions) have so responded to the treatment as to become reasonable risks for operation and have been operated on for enlarged prostates, and discharged well, so far as the operative condition was concerned; and in no instance, in the last two years, has there been a case of post-operative uremia.

In the preparation of patients with renal disturbance, produced by back pressure from obstruction to urination, the first essential is to relieve the obstruction. In the case of prostatics with residual urine this, in most instances, can be satisfactorily effected by the insertion of a retention catheter in the bladder. This may be allowed to drain by a rubber tube connection directly into a bottle beside the bed, or the catheter may be stoppered with a cork and the bladder emptied every two to four hours by the patient or an orderly. The care of the catheter is important. As a routine measure the bladder is irrigated twice daily with boric acid, and every third or fourth day the catheter is removed, cleaned and boiled, and left out for several hours, the urethra, meanwhile being irrigated. In some cases a retention catheter cannot be borne by the patient owing to a sensitive urethra or bladder from stone, infection, polypus, etc. A few of these cases may be prepared by periodic catheterization every four to six hours; in others, a rapid suprapubic cystotomy is demanded in order to establish free drainage.

A valuable adjunct in the preparatory treatment of these cases is the administration of urinary antiseptics. Of these, hexamethylenamin is the best, and is given three times a day after meals in 15 grain doses to all cases. The urine reaction is watched, and when faintly acid or alkaline acid sodium phosphate, up to as much as 120 grains three times a day before meals, or sodium benzoate, from 15 to 40 grains, is given, in order to insure the conversion of the drug into formalin. As a matter of fact hexamethylenamin is given in this way as a routine procedure in all urological cases, both as a prophylactic and curative measure, and should not be mentioned as confined, in particular, to prostatics. Where the urine is alkaline, hexamethylenamin is useless, and boric acid, in 15 to 30 grain doses with one of the acid-producing drugs just mentioned, may be given until the urinary reaction changes.

Familiarity with the significance of infection in cases with residual urine is of considerable importance. A prostatic who has been long using a catheter and has a chronic cystitis in consequence, is a much safer risk than another prostatic who comes with a large amount of residual urine, has never been catheterized and has an uninfected urine. In the former case an immunity and a certain degree of resistance to the infection have already been acquired; in the latter case, in whom the danger of infection either from a beginning catheter life or following the operation is extremely grave, an acute infection added to the operative burdens may greatly increase the risk. The case should be put upon preliminary catheter treatment to accustom the urinary tract, both kidneys and bladder, to the unusual condition of freedom from residual



urine, and, if infection occurs, to give time for the acquisition of an immunity to catheter infection. The gradual reduction in the amount of residual urine in the attempt not to relieve the kidneys too suddenly has not been found practicable or at all necessary in this clinic. A second essential in the treatment of these cases is to force the intake of water. Unless contraindicated by associated uremic conditions, as above mentioned, each case should get from six to eight ounces of water every hour. Where the water is not taken well by mouth it should be given per rectum by the Murphy method, or by rectal feeding every two to four hours, according as it is retained, or, if necessary, by repeated infusion. The improvement of such cases as indicated by the phthalein tests and clinical symptoms is sometimes remarkable, when put upon forced water feeding combined with the use of a retention catheter. The water flushes the stagnant kidney stimulating it to increased activity and in addition, in certain cases, seems to act as a medium for the excretion of waste accumulations. This is particularly noticeable in some cases with nitrogen retention from injury due to back pressure without pronounced nephritis, the urea and other nitrogenous substances being excreted in increased amounts with an increase in water output. An old man, 81 years old, weak, nervous and miserable, on admission, recently with 1300 cc. of residual urine and a phthalein output of only a trace in three hours and 18 minutes, and almost two grams of blood urea to a liter, in less than two weeks, under the above routine, became strong, cheerful and active. His phthalein had increased to 30 per cent in two hours and there were only about 600 mg. of urea to the liter of blood.

The preparatory care of surgical kidney, other than to definitely fix the diagnosis, is rarely indicated, as cases of surgical kidney demand operation as direct treatment for the condition, and the risk is, therefore, purely operative. Owing to the occurrence of troublesome obstipation or pseudoparesis of the bowels following kidney operations, the result, possibly, of trauma to the sympathetic centers from traction on the renal pedicle, a routine preparation of all kidney cases has been instituted. Within the last two years there have been three cases on whom colostomies had to be performed for this complication. All cases are now given an ounce of castor oil the night before the operation, an enema in the morning

and 1/50 gr. eserine hypodermatically one-half hour before going to the operating room.

The preparation of cardiac cases for operation may be briefly stated. Lack of compensation, marked fibrillation and acute conditions contra-indicate operative intervention, except where it becomes absolutely necessary. Rest in bed, regulation of the fluid and food intake, and the judicious use of digitalis and strophanthin constitute the preparatory treatment. Chronic passive congestion of the kidneys may occur in these cases, and be of such degree as to produce marked reduction in function. Improvement in the renal condition with betterment of the cardiac symptoms, indicates that the heart is responsible for the kidney disturbance.

In cardio-renal risks combined cardiac and renal studies are directed towards the determination of which factor, heart or the kidneys, is the more responsible for the severe symptoms, and the proper treatment instituted accordingly.

Cases of hypertension occur with, apparently, no cardiac or renal disturbances. Hypertension, in itself, is no contra-indication to operation, but it is well to allow these cases a few days of rest in bed and a lowering in blood-pressure frequently follows. The administration of drugs, as nitroglycerine, the nitrites, etc., is rarely indicated and, very frequently, strongly contra-indicated. Blood-pressure and cardiogram records before, during, and following operation show a fall of the pressure during the operation, when nitrous-oxide-oxygen-ether anesthesia is used. Several cases have been operated upon in the lithotomy (head-down-position) which tends to increase pressure, with a pressure of over 210 before the operation in which not a single complication, due to hypertension, has resulted.

Acute infections of all kinds are definite operative contra-indications, unless the operation is directed primarily against the infection, as in an acute septic kidney, or an epididymectomy for suppuration of the epididymis. The danger of sudden recurrences in the presence of chronic infections should always be carefully considered. Chronic infections of the urinary tract demand careful watching to prevent their becoming acute, and urinary antiseptics, bladder and urethral irrigations and even ureteral and pelvic lavage, when indicated, should be rigorously followed.

## EXPERIMENTAL HYDRONEPHROSIS.

By N. M. KEITH, M. D.

Early this year, Dr. Snowden and myself undertook the study of experimental hydronephrosis in dogs at the suggestion of Drs. Rowntree and Geraghty. It was found on examining the work of previous investigators that the subject had been approached from both pathological and physiological standpoints. The methods of the former were confined chiefly to the study of histological changes in the kidney following complete or partial ligation of the ureter, while the physiological studies consisted in determining functional disturbances due to back pressure of a few hours on the renal pelvis. Our

aim, however, was to study renal activity over a considerable period of time, following the production of hydronephrosis.

There seemed to be three general methods of producing a hydronephrosis in dogs: First, to obstruct the urethra partially, thus simulating the common clinical condition of hypertrophied prostate; second, to obstruct both ureters partially; or, third, to obstruct one ureter partially and remove the opposite kidney. The third method was adopted after a few preliminary experiments.

It has been known since 1859 that a back pressure on the



kidney of over 45 cm. of water very soon leads to a complete cessation of function. Therefore, our idea was to produce a back pressure between 15 and 30 cm. In order to determine the amount of obstruction necessary to produce such a pressure, a cannula was inserted high up into the ureter of a recently sacrificed dog and bands of various material, *e. g.*, pieces of rubber and silk catheters and ordinary elastic rubber, were placed about the ureter just above its entrance into the bladder. The most satisfactory means of producing a partial obstruction which would develop the necessary back pressure was furnished by the use of an ordinary elastic band 1 mm. in thickness, held in place by a silk ligature.

Having obtained a method that gave promise of success, we operated upon a dog under aseptic technique; the left kidney was removed and an elastic band was fastened about the right ureter 2 cm. above its bladder orifice. The animal was watched closely from day to day for one week and appeared on casual observation to be normal—eating and jumping about as usual. At the end of the week, the dog was sacrificed and a definite hydronephrotic condition of the right kidney was found. The back pressure developed, as shown by a water manometer, amounted to 30 cm. thus permitting functional renal activity. Having obtained an experimental procedure which seemed to warrant success, we next made daily functional studies following the operation.

The functional tests employed were: (1) The daily intake of nitrogen in the food and output in the urine; (2) the phthalein test of Rowntree and Geraghty; (3) the lactose test; (4) the phloridzin test as advocated by Roth, and (5) the urea and total non-protein nitrogen content of the blood according to Marshall's and Folin's methods.

A typical clinical course was generally observed after operation. The animals took food readily and appeared lively after 24 hours and seemed normal except for an increased output of urine of a low specific gravity. The dogs remained in this condition although definitely losing weight for from three to four weeks when toxic symptoms developed rather abruptly. These consisted of inability to take food, vomiting and lassitude, followed in three to four days by exitus. During this latter stage, a comatose condition or convulsive movements were never observed.

The chief functional changes were briefly, as follows: The phthalein output on the third or fourth day showed a moderate diminution, the excretion of the dye usually amounting to 35 to 40 per cent in two hours. At the same time the non-protein nitrogen in the blood increased to four times the normal

amount. The lactose and phloridzin tests showed only slight deviations from the normal. From the fourth day until the development of toxic symptoms, three to four weeks later, the renal function as indicated by the above tests remained almost stationary, though at times the urinary output of nitrogen exceeded the nitrogen in the food. This latter observation would seem to indicate that the increase of the non-coagulable nitrogenous constituents of the blood is not only due to a renal retention, but also to a metabolic disturbance which results in an increased nitrogen catabolism.

With the onset of the terminal toxic symptoms, the renal function showed severe impairment along with a rapid rise in blood nitrogen. The non-protein nitrogen reached as high as 3 grams to the liter before death.

To sum up, the important changes noted after submitting dogs to the procedure outlined were: (1) A definite increase in the blood nitrogen without marked renal functional disturbances or untoward clinical symptoms, for a period of three to four weeks; (2) a high nitrogen output as compared to the intake; (3) a terminal condition of a few days marked by severe renal insufficiency.

The question naturally arises whether infection of the lower urinary tract played a part in producing the condition described. All of the animals which developed the terminal toxic condition showed an infected kidney at autopsy. To determine whether this factor played a part in the initial disturbance, two animals were sacrificed within 10 days of the operation and no evidences of infection were found on histological examination. Therefore, at present we think that back pressure on the renal parenchyma produces the condition outlined above.

An endeavor to treat the condition by removing the elastic band has not as yet been carried out. The only therapeutic measure attempted was the effect of venesection and infusion on the amount of blood nitrogen. One dog, after the withdrawal of 225 cc. of blood, received an infusion of the same amount of a mixture containing defibrinated blood and normal saline. The blood showed a remarkable drop in the non-protein nitrogenous elements, for within 24 hours the blood urea diminished from 1.8 to .55 gram per liter and remained at this lower figure for three days. This fact would seem to indicate that phlebotomy and infusion or the new method of plasma withdrawal (plasmapheresis) as introduced by Abel, Rowntree and Turner, have practical applications in cases with lower urinary tract obstruction and retention of nitrogen in the blood.

## THE JAMES BUCHANAN BRADY UROLOGICAL INSTITUTE.

By HUGH H. YOUNG, M. D.,

*Clinical Professor of Urology, The Johns Hopkins University.*

In the summer of 1912 the writer showed to Mr. James Buchanan Brady tentative plans for a building to be devoted to urological surgery, and without much urging Mr. Brady decided to build and maintain such a building at The Johns Hopkins Hospital. The tentative design consisted of a six-story building to connect with and utilize the present excel-

lent out-patient genito-urinary dispensary, with public and private wards, adequate laboratories and rooms for research and experiment, and quarters for residents.

Authorized by Mr. Brady to design a building to cost about \$200,000, we first made a cursory study of hospitals here and abroad, but could find only one—St. Peter's, in London—



solely devoted to urology. Then with the kind assistance of Dr. Winford Smith, superintendent of The Johns Hopkins Hospital, Archer & Allen, architects, and C. L. Reeder, engineer, we proceeded to perfect the plans and specifications for a building in which the laboratory and experimental side should play a very important rôle, and in which clinical material, public and private, out-patient and in-patient, could be used for study, research and advancement in the field of urology and border-line subjects. The accompanying reproductions of some of the plans show the fruition of our labors of over a year.

The building consists of seven stories, with a basement. The location was determined by a desire to be adjacent to and to connect with the "urological out-patient dispensary" in the first floor of the surgical building. For this purpose there was a space of about 120 feet between the surgical building and the kitchen on Monument Street, in which a building 45 feet wide has been designed to go.

It was considered very important that the entrance should connect directly with the main corridor which connects the various wards of the hospital, and this has been very successfully provided for by using a portion of the north end of the basement of Ward D as a corridor and broad entrance hall from which the stair case and elevator are reached. As the main corridor is on high ground, it has been possible to get two stories beneath this level, the first floor which connects with the urological out-patient dispensary being on a level with the street; and the basement which will be well lighted from the outside in the manner described later.

On the west side the building is connected with the kitchen by a bridge through which food will be brought directly to the dumb-waiter supplying the five floors above. This will make it unnecessary to enter the building with food wagons, etc., the food elevator being loaded from without—a great desideratum. The proximity to the surgical building, the out-patient dispensary, the kitchen and the main corridor will make for simplicity and ease of management.

The basement contains rooms for animal experimentation. In order that no smell or noise shall get beyond the rooms in which the animals are kept, fresh air is to be forced in at the ceiling (after passing over steam coils) and then to be drawn out by other fans through registers near the floor. In this way a healthful atmosphere can be maintained without opening the windows. Adequate operating and preparation rooms are provided, with apparatus for sterilization, etc.

A workroom, to be fitted up as a well-equipped machine shop, is intended to be used in the preparation of experimental apparatus and new surgical instruments. The machinist in charge will be of great service in many of the activities of the institute. The rooms above described are provided with abundant illumination by cutting away the surrounding embankments to the form of gradual terraces, so that the light is not obstructed.

The remainder of the basement, the west side and south end, will serve valuable utilitarian purposes, providing: a room for soiled clothes, which will reach it by chute from the

upper floors of the building; a dry room provided with steam for drying bed clothes, mattresses, etc.; a room for the storage of trunks; a clothes room with individual lockers for patients' clothes; rooms for storage of mattresses and apparatus; and a long storeroom which will connect with the storerooms of the kitchen building by means of a tunnel and lift.

The first floor is to take care of varied activities. A waiting room for patients to be admitted to the hospital will be found on this floor. Rooms for clinical purposes, history taking, consultation and examination are amply provided for. There will be five rooms for general urological examinations, including urethroscopy, cystoscopy and ureter catheterization. Each room will have hot and cold sterile water (provided from a general system) for the preparation of irrigations, an electric sterilizer for instruments and nozzles, sink, lavatories, etc. Two of these rooms are adjacent to X-ray apparatus so that radiographs, pyelographs, high-frequency treatments, etc., can be taken without moving the patient from the cystoscopic table. Specimens removed from patients for urinalysis or histologic diagnosis may be studied in the adjacent laboratories, and X-ray plates may be developed and studied in rooms provided for this purpose.

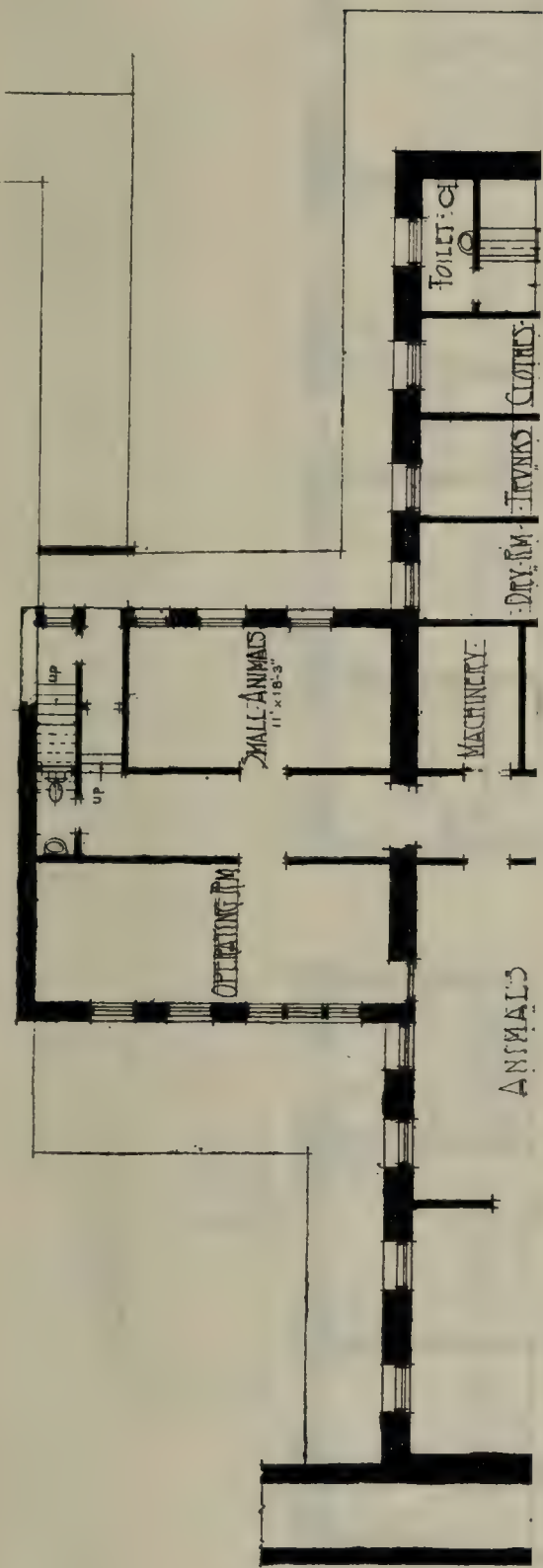
The laboratories on this floor are intended to be very complete and adequate for a small group of workers. The preparation room with hoods, cupboards and storeroom will be the work place of one or more technicians. The clinical laboratory will be used for urinalysis, blood work, etc. Laboratories for bacteriology, pathology and chemistry, and three or four rooms for private research are provided. These taken in conjunction with the rooms for animal experimentation in the basement should offer good opportunities for investigation. The various laboratory rooms are to be equipped with vacuum and compressed air, and the three chemical hoods will also have steam connections. Running water and small staining sinks on the microscopic tables will add to the convenience of the workers.

This laboratory floor ties in well with the urological out-patient dispensary, which, having recently been rearranged and remodeled as will be seen here, is very commodious and well adapted for a large out-patient clinic. The general clinic room holds six operating tables, besides two places for standing irrigations, sterilizing apparatus, etc. Adjacent is a clinical laboratory in which urinalysis, bacteriological work, and study for spirochætæ are made. Another room provides a place for minor operations, and next comes a room for urethroscopy and cystoscopy. A lecture room and a small teaching museum complete the floor which connects with the two-story wing of the Brady Institute.

Important and interesting cases, discovered in the out-patient department, will be brought across and thoroughly studied in the examining rooms and laboratories of the institute, and if necessary ureter catheterization, functional renal tests, radiographs, pyelographs, etc., will be carried out, before or after admission to the hospital wards.

It is the intention thus to use the hospital residents and internes, and a selected group of outside workers in all the





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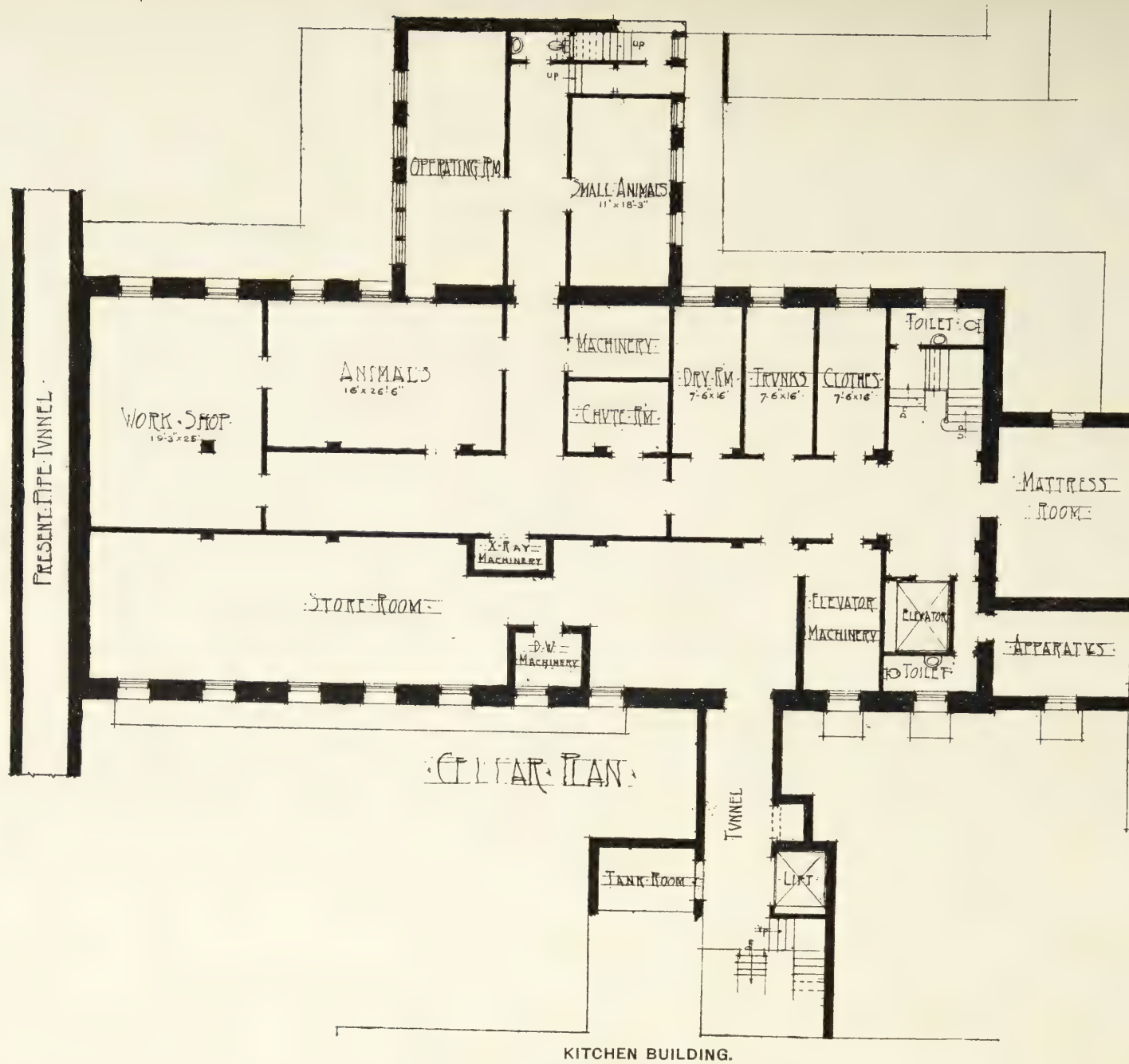


FIG. 1. THE JAMES BUCHANAN BRADY UROLOGICAL INSTITUTE.

Plan of basement. The larger part of this floor is to be used for storage purposes. A portion beneath laboratory wing and at north east corner is to be used for animal experimentation, operations, etc. A well equipped machine shop is to be provided. The X-ray machine is here.

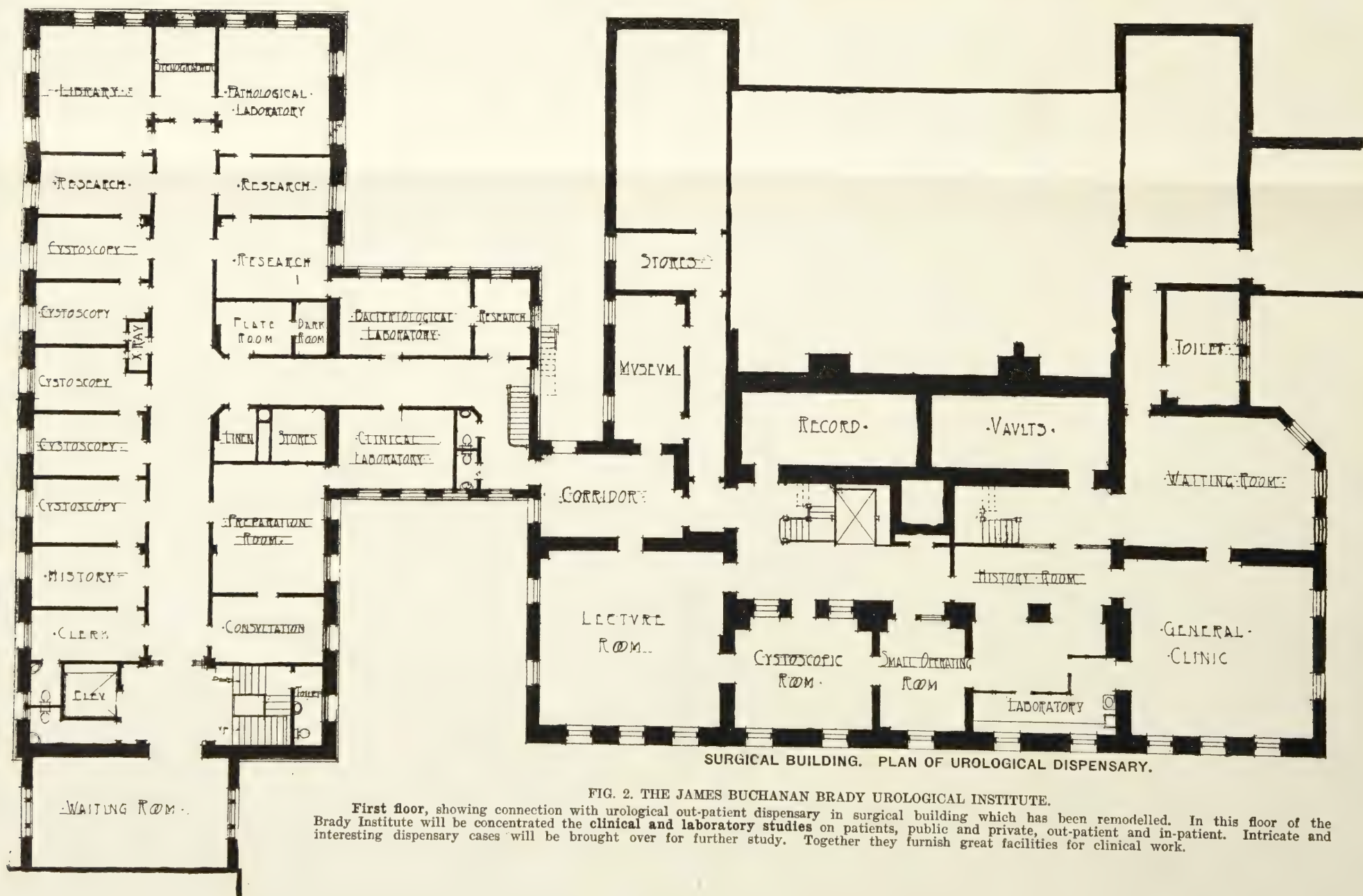


FIG. 2. THE JAMES BUCHANAN BRADY UROLOGICAL INSTITUTE.

First floor, showing connection with urological out-patient dispensary in surgical building which has been remodelled. In this floor of the Brady Institute will be concentrated the clinical and laboratory studies on patients, public and private, out-patient and in-patient. Intricate and interesting dispensary cases will be brought over for further study. Together they furnish great facilities for clinical work.



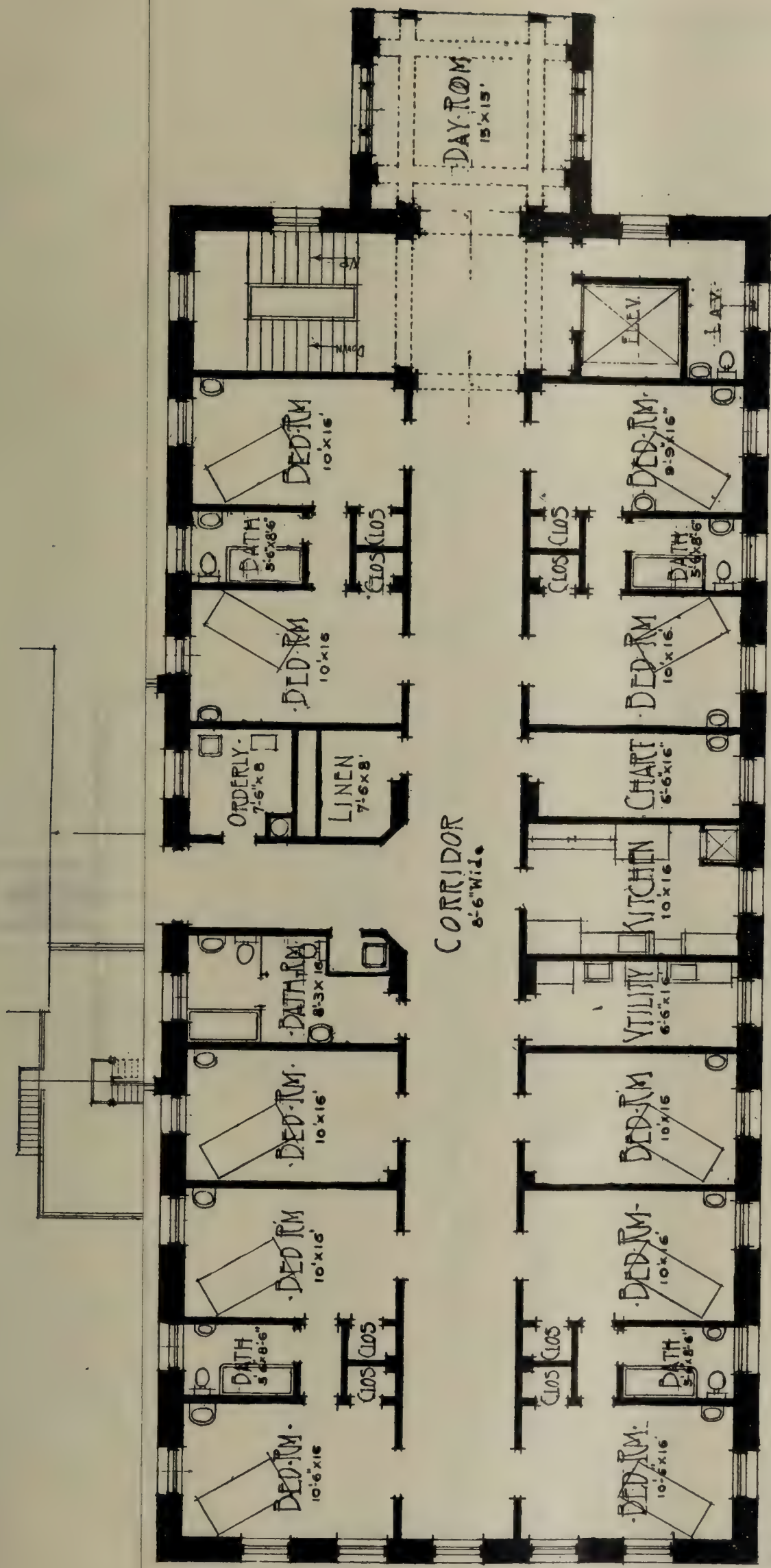


FIG. 5. THE JAMES BUCHANAN BRADY UROLOGICAL INSTITUTE.

Fourth floor: Private ward with ten bed rooms, of which eight are arranged en suite, two rooms with intervening bath connecting corridor and clothes closets. The utility room on each floor is provided with a system of hot and cold sterile water.



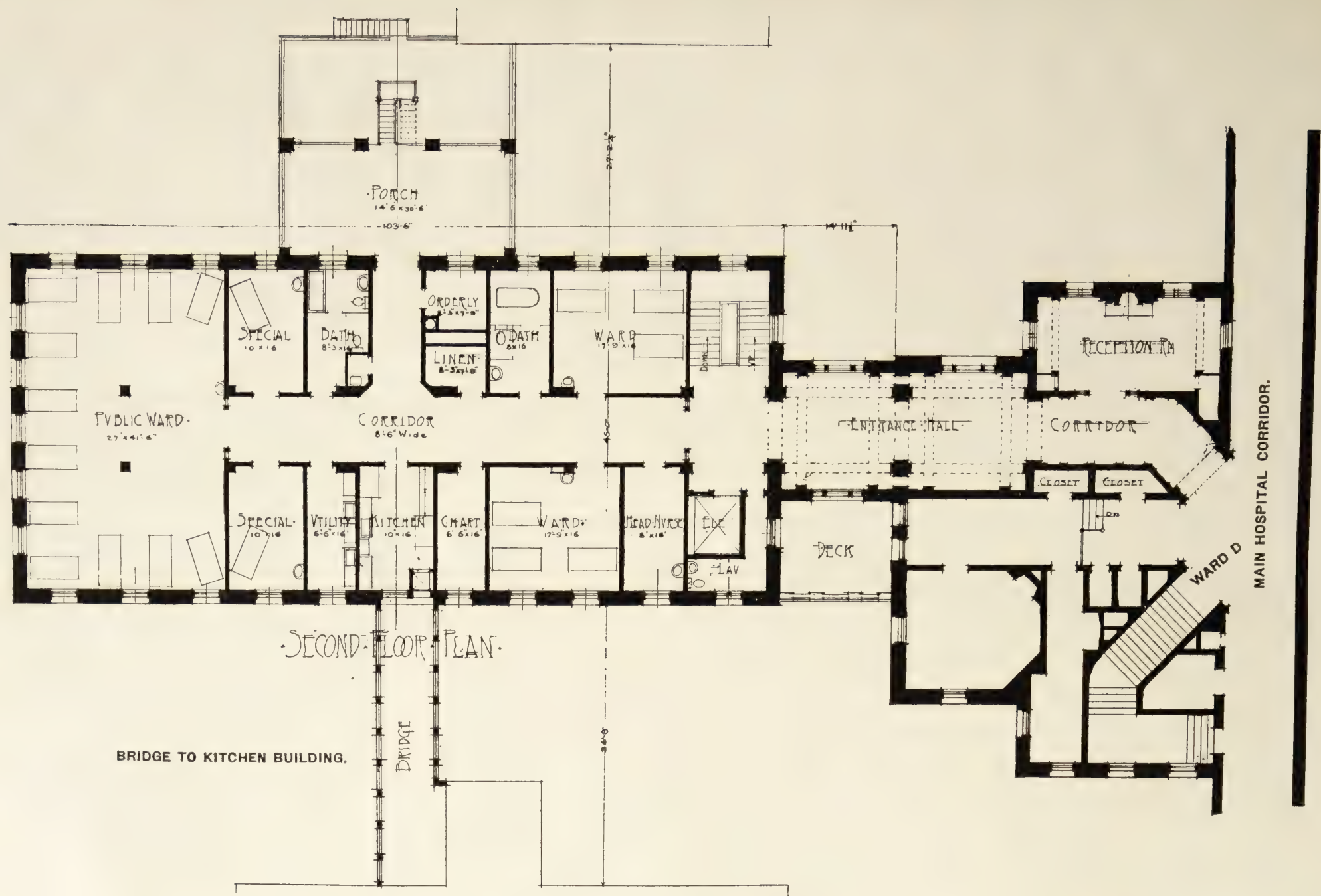


FIG. 3. THE JAMES BUCHANAN BRADY UROLOGICAL INSTITUTE.

Second floor: Entrance hall and corridor connecting with main hospital corridor beneath Ward D (remodelled to provide this). This floor provides a public ward of 20 beds, with five subdivisions of varying number of beds to facilitate research by segregation and isolation of groups of patients. Note centralization of work rooms; lavatories in all wards; porch and roof.

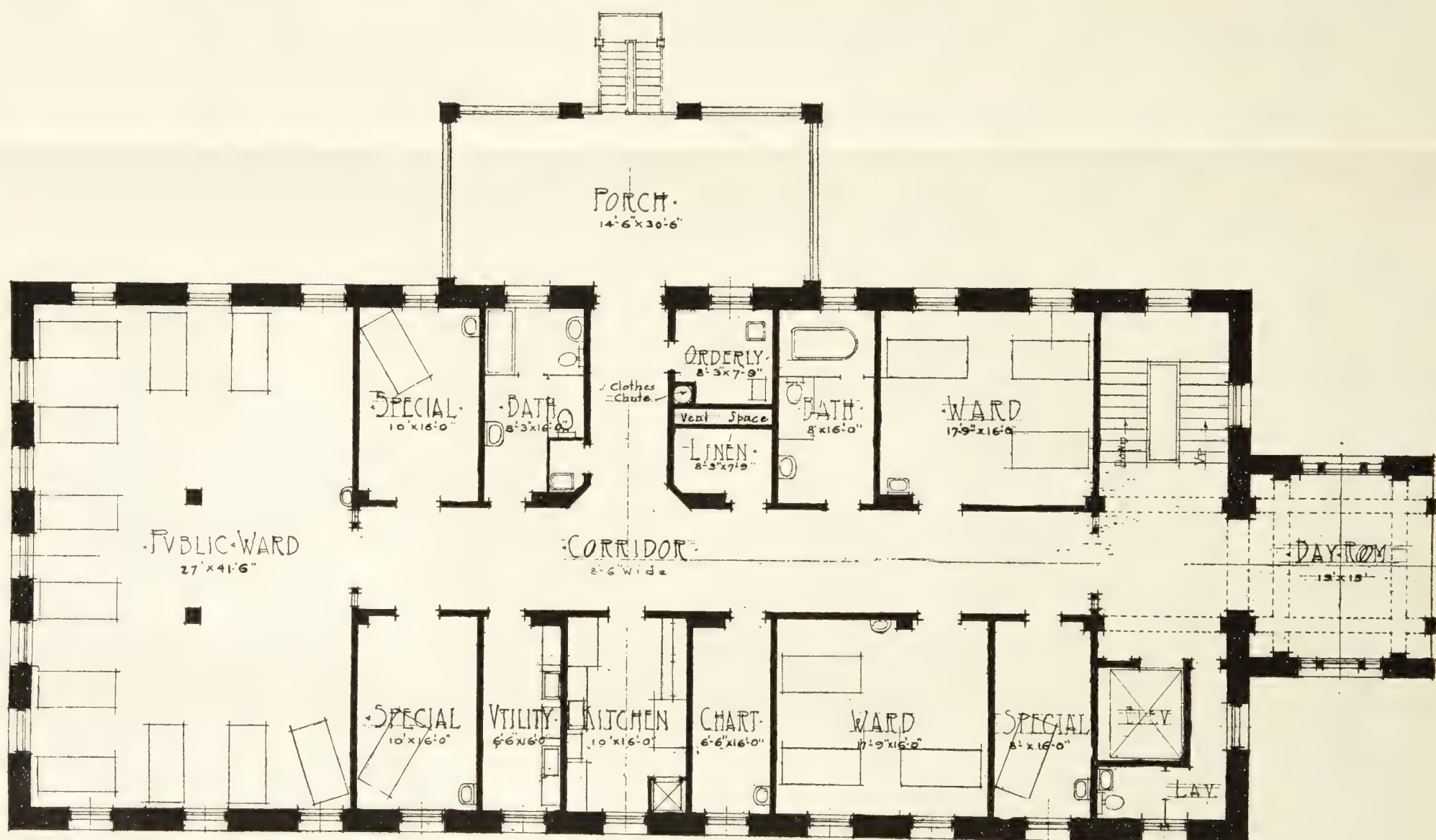


FIG. 4. THE JAMES BUCHANAN BRADY UROLOGICAL INSTITUTE.

Third floor: Public ward of 20 beds similar to second floor. Over entrance hall on floor below a sitting or "day" room is obtained. A cloak room and lavatory for nurses is provided behind elevator shaft. The utility room, charting room, orderlies' room, and maids' closet provide unusually complete working facilities.

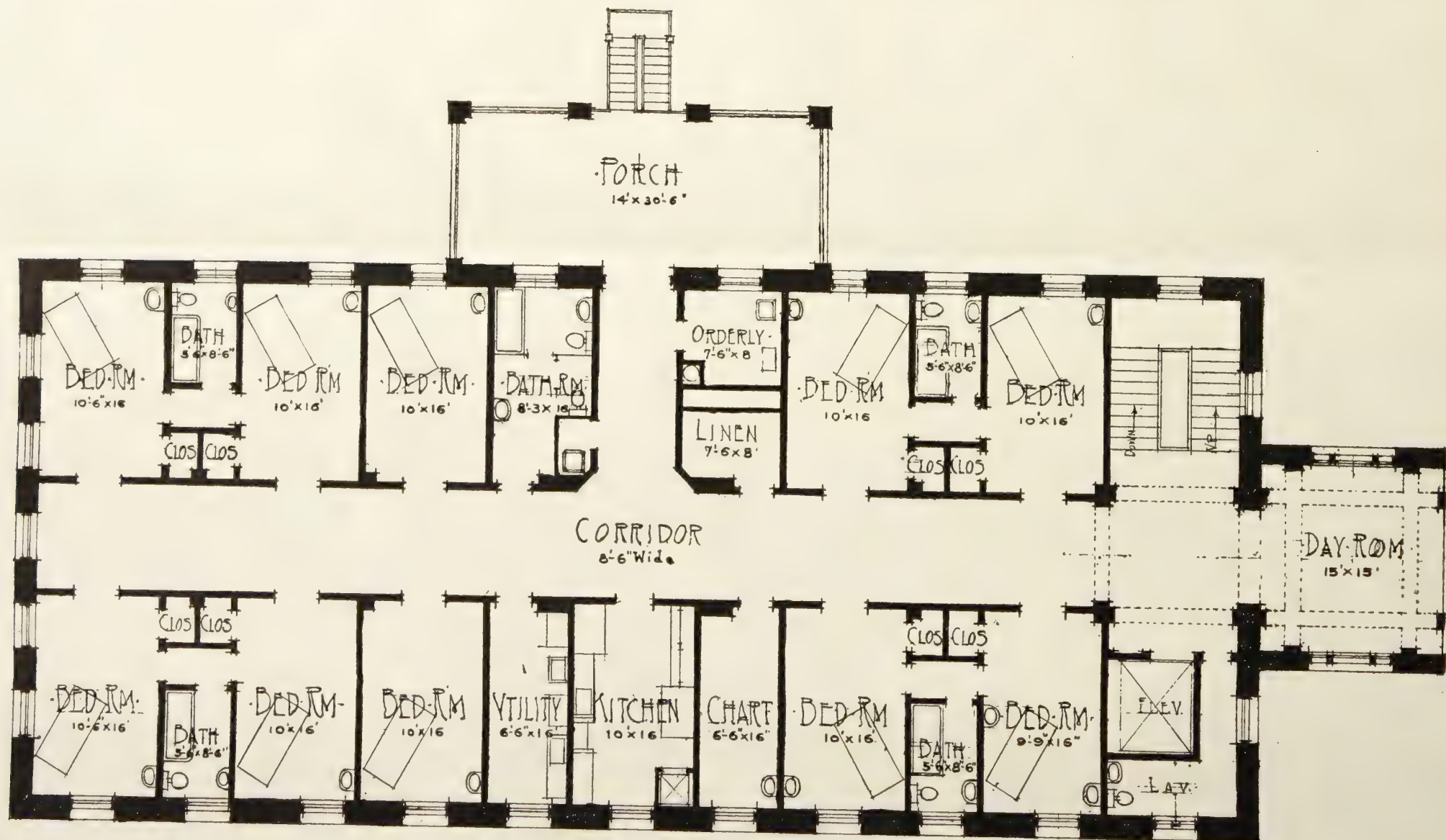


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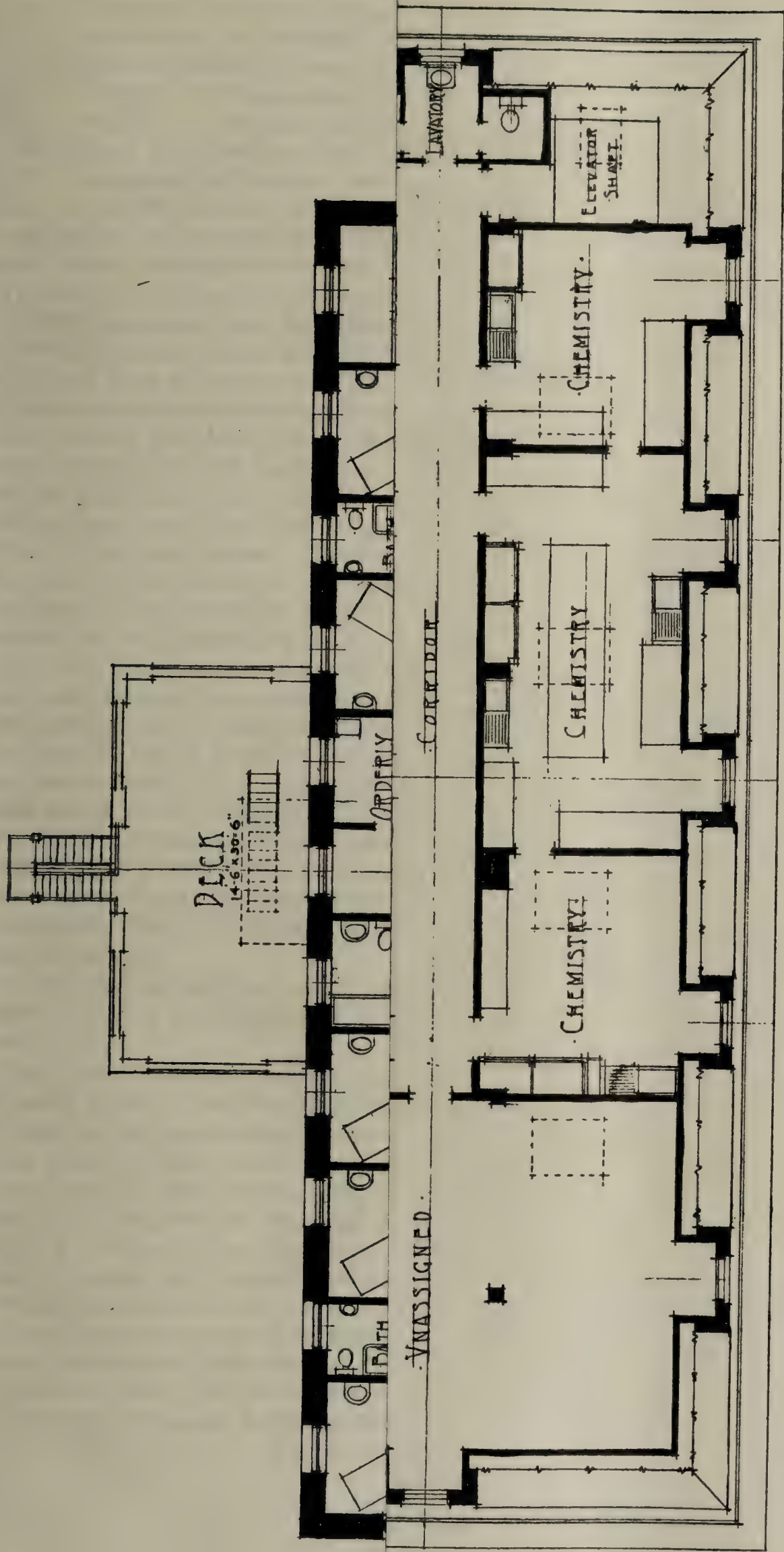


FIG. 8. THE JAMES BUCHANAN BRADY UROLOGICAL INSTITUTE.

Seventh floor: Research laboratories. Besides a well equipped chemical laboratory, we expect to have the other rooms equipped for special research workers in pathology, physiology, physics, experimental surgery, etc. Skylights provide excellent illumination. This floor in conjunction with the clinical laboratories on the first floor and the animal laboratories in the basement should serve to emphasize and foster spirit of research in the Brady Urological Institute.



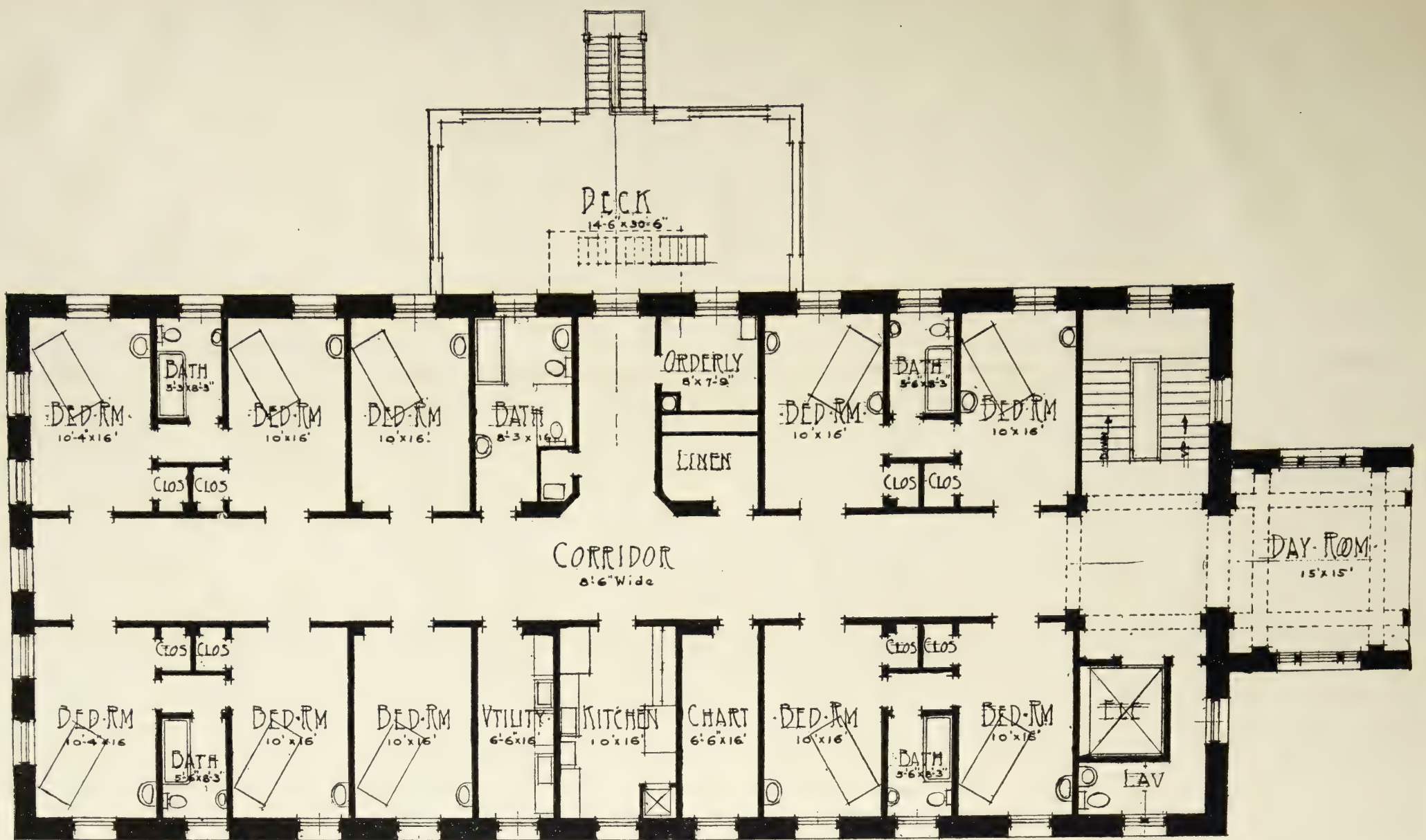


FIG. 6. THE JAMES BUCHANAN BRADY UROLOGICAL INSTITUTE.  
Fifth floor: Private ward with ten bed rooms. The centralization of utilities is the same on the private and public wards.

FIFTH, SIXTH AND SEVENTH FLOOR PLANS.

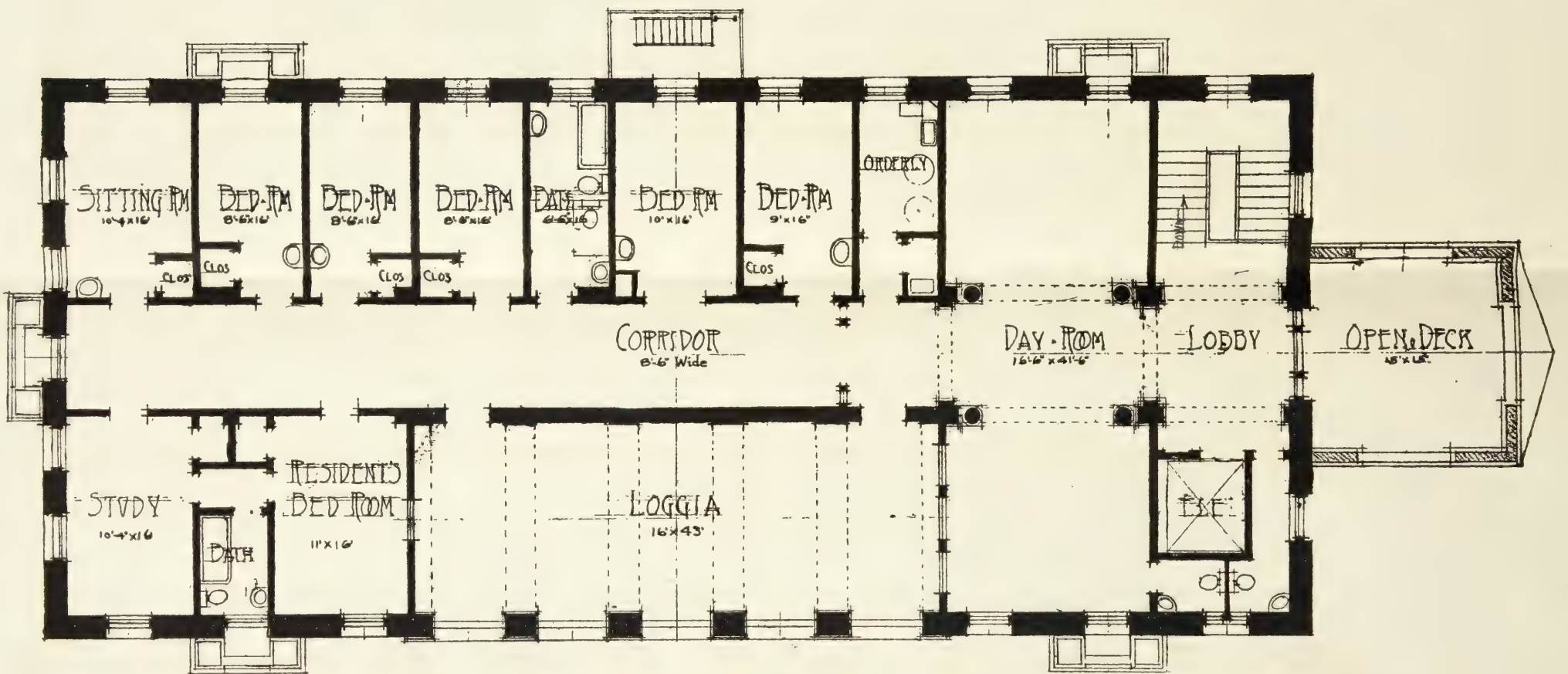


FIG. 7. THE JAMES BUCHANAN BRADY UROLOGICAL INSTITUTE.  
Sixth floor: Recreation rooms for private patients, roof deck, enclosed porch ("loggia") and day room, affording additional space for convalescence out of doors, etc. Residents' quarters (for six) occupy the remainder of this floor. Sterile filtered water, prepared on this floor, is piped to the wards, utility rooms, and the cystoscopic rooms on first floor and in dispensary.

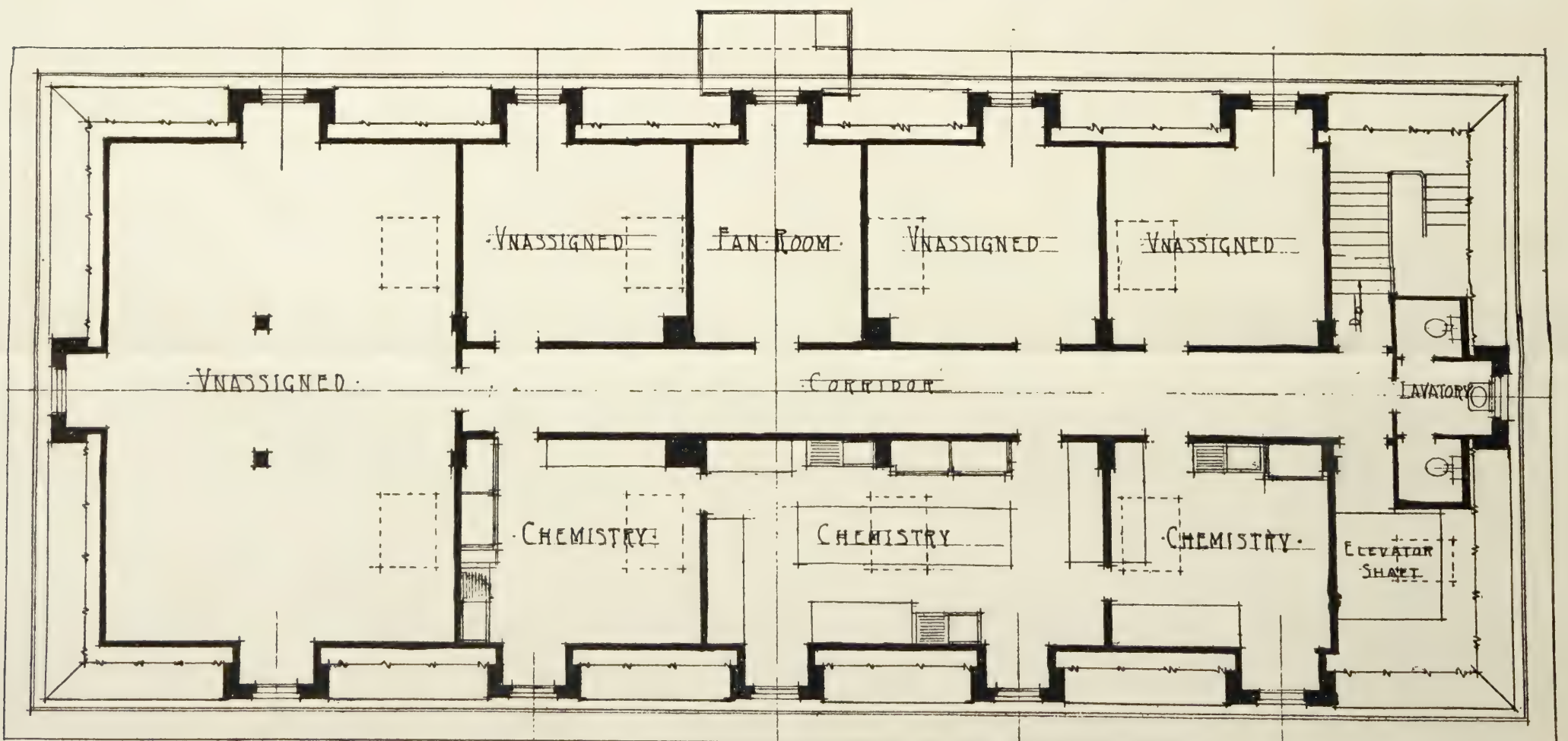


FIG. 8. THE JAMES BUCHANAN BRADY UROLOGICAL INSTITUTE.  
Seventh floor: Research laboratories. Besides a well equipped chemical laboratory, we expect to have the other rooms equipped for special research workers in pathology, physiology, physics, experimental surgery, etc. Skylights provide excellent illumination. This floor in conjunction with the clinical laboratories on the first floor and the animal laboratories in the basement should serve to emphasize and foster spirit of research in the Brady Urological Institute.



various departments at different times of the day, viz.: dispensary, laboratories, research rooms, animal experimentation, hospital examinations and treatments on public and private patients, work in the operating room, in the surgical building and in the wards. This concentration of various activities should do much to save time, facilitate thorough work, bring all the workers into close touch with each other, inspire a spirit for experiment and research, and insure a full utilization of all the clinical material at hand. We have already secured several well-trained, whole-time laboratory men to lead in research and experimental work.

The second story contains a public ward for twenty patients, subdivided into a large ward for twelve patients, two single-bed wards for special cases, and two small wards of three beds each. Each ward is provided with a lavatory, and there are two bath-rooms and toilets for general use. In this way cases can be isolated for special study. The service rooms are grouped at the center of the building which should facilitate administration. The provision of both utility and charting rooms, and also a special room for the orderlies' work are rather novel features. The food lift is reached from the outside of the building on this floor by a flying bridge from the kitchen, thus doing away with the necessity of bringing the food wagons into the building.

The main entrance is also on this floor, the connection being made with the main hospital corridor, by means of a short corridor, and a dignified "foyer" or entrance hall. This room, 15 feet by 34 feet in size, is finished in panelled gray marble, and in it a bronze dedicatory tablet to Mr. Brady will be placed. Lighted by French windows on each side, and with a few attractive chairs and settles here and there, it should prove a pretty feature. To one side is a reception room. From this hall the second public ward is reached by a single stair flight. An elevator serves the private wards and roof garden.

An office for the chief nurse of the building is next to the entrance lobby—a convenient point for administrative purposes.

The third story is similar to the second—a public ward for twenty patients. Over the entrance hall of the floor below, the plans call for an attractive day room.

The fourth and fifth stories each contain rooms for ten private patients. One public and four private baths are provided. The latter may be used with either or both of the adjoining rooms, which may likewise be used *en suite*. Every room is provided with lavatory and running hot and cold water—which should prove a great convenience to patients, nurses and doctors, and greatly minimize the danger of transmitting infections to other rooms. The same grouping of service rooms, seen on the public ward plans, are shown here, and day room and porch are also provided.

The corridor floors are to be of battleship linoleum with a

broad border of gray marble, and a coved marble base, both on the private and public ward floors, a feature which is copied from the Marburg Building. In the laboratories terrazzo is to be used, as also in the examining rooms, except the two in which X-ray work is to be done, and in these sheet rubber will be employed to minimize danger of electric shock, and also for comfort. The private bed-rooms will have wood floors of Georgia pine.

The sixth floor is primarily for residents' quarters. The chief resident will have his study, bed-room and private bath; the others each a bed room with lavatory and running water, and the use of a conjoint sitting-room. The rest of this floor is to be used as a day time sitting and lounging place for private patients, a large day room, an open porch or "loggia," and a deck or roof garden being provided.

The seventh floor is arranged to provide laboratories for research. It is generally agreed that these should be separate from the clinical laboratories, and the top story thus provides an ideal place for this purpose. Good over-head light is provided by skylights. The west side is already equipped for chemical work, and it is hoped soon to have the other rooms amply equipped for other research work, including pathology, physiology, physics (which concerns so many urological problems), border-line subjects between medicine and urology. The workers are already at hand and waiting.

No operating rooms for patients are provided, as ample accommodations are present in the surgical building. The building will be of the best modern fireproof construction, and will cost \$215,000. The furnishings and equipment will cost \$20,000 more. Ample maintenance has been furnished by Mr. Brady. Built of brick to correspond with the other buildings of the hospital group and with base and trimmings of bluish stone, it will form an attractive addition and add another complete unit for a special subject, of which the Henry Phipps Psychiatric Clinic and the Harriet Lane Home for Children, which have recently been opened on the grounds of The Johns Hopkins Hospital, are such excellent examples.

These self-contained units, with wards for public and private patients, laboratories clinical and experimental, and outpatient department, should prove a wonderful stimulus for research and advancement in the special subjects to which they are dedicated.

ADDENDUM: The proposed organization of the Brady Urological Institute is as follows:

Director,	Research Staff:
Assistant Director,	Pathology, Assistants in
Clinical Staff,	Chemistry,
Chief of Dispensary,	Border-line Problems Between
Assistant Chief of	Urology and Medicine,
Dispensary,	Problems Involving Physics and
Resident Urologist,	Experimental Surgery.
Five Assistant Residents.	



## PSYCHIATRY.

### EXTRA-MURAL PSYCHIATRY IN BALTIMORE.

By WM. BURGESS CORNELL, M. D.,  
*Executive Secretary, Mental Hygiene Committee.*

One of the most marked advances in psychiatry of the past 10 years is the realization that the major portion of the life history of the average mental patient transpires beyond the hospital walls.

The hospital, to be sure, plays an indispensable rôle in sheltering the patient during the active phase of the psychosis, when he may be dangerous to himself or to society, and in administering curative measures in ways and means otherwise impossible outside of an institution. But before the hospital is reached, a great deal has transpired in a given case, and just as truly a great deal happens after discharge from the hospital. That is, there are two separate and very important phases in the life history of the patient in which the hospital residence may be conceived as an intermediate period which is often hardly more than a biographical cross-section. It is these two phases, the pre-hospital and the post-hospital which form the field for extra-mural psychiatry, and to these your attention is directed, taking up the latter or post-hospital first.

The appreciation that hospital service in general medicine and surgical diseases often needs to be augmented by treatment or supervision after leaving the hospital, led to the establishment of the social service and this same sort of outside supervision has come to be extended to the neurologic and psychiatric clinics.

We well know there is no group of diseases of longer average duration and more disturbing and disabling to the individual and more costly to society than those we term nervous and mental. Hospitals and clinics, whether state or private, cannot often detain a case throughout the long period sometimes necessary to insure complete convalescence, particularly where the recovery is only partial; thus arises immediately need for after-care supervision in instances where the family is unable to supply the necessary care. Shall such cases incapable of maintaining an independent existence be turned adrift and allowed again to breakdown, all too soon? Every principle of constructive economy demands that this be prevented if possible. After-care supervision has become a necessary adjunct to every hospital and clinic receiving nervous and mental cases; particularly is this true of state hospitals where the large majority are wage earners, who, through the disabling nature of their disease, may quickly become dependent upon the state.

Briefly what does after-care aim to accomplish? First of all to complete convalescence and to postpone as long as possible, or prevent a return to the hospital. Environment and its relation to the patient are studied, and when necessary adjusted with a view of obviating further trouble. After-care also permits some persons to leave the hospital, who could not otherwise be discharged. It is also a safeguard to society, as

many a deed of violence and public disturbance which often occurs with relapses or recurrent attacks may be obviated by careful after-care supervision. Lastly one of the most important results of such a system is a large financial saving to the state.

All of the advantages which have been bespoken for after-care supervision are equally true for the pre-hospital phase. This involves the exercise of preventive and prophylactic measures and aims at checking the disease if possible in the early stages by recourse to the use of general hospitals or other measures and preventing, if possible, a commitment to state institutions.

Furthermore, this question of prophylaxis is intimately connected with every ramification of business, social, school and family life. The difficulty is how to reach the cases where such effort can obviate the grim consequences so disastrous to the individual and costly to the state. Prevention represents the only way the numerical increase of mental disease and mental defectives may be checked, and yet nowhere has any one more than scratched the surface of this most promising field of endeavor.

Maryland, along with other states, each year spends millions of taxpayers' money for hardly more than custodial care of the insane and this applies also to the feeble-minded, delinquent and criminal, while by comparison hardly a cent is expended for preventive measures.

It is time to turn our efforts toward this side of the question, and to arouse public as well as scientific interest in this new standpoint and new endeavor.

Without arguing the question as to the existence of an actual increase in insanity, in Maryland, as elsewhere, we are apparently always building new institutions which are always overcrowded, and always have a long waiting list for admission. If this alone is not sufficient evidence of the need of prophylaxis, a trip through the crowded chronic wards of any of our state hospitals and the sight of hundreds of helpless, hopeless human derelicts, who seem mutely to plead for the establishment of preventive psychiatry, will add all that is needed from a humanitarian standpoint.

The Mental Hygiene Committee in Baltimore, organized through the efforts of Dr. Adolf Meyer and Dr. A. P. Herring, was established for constructive work in both preventive and after-care fields. In a little over a year and a half, 600 cases, representing many phases of each division, have been referred to the committee for study, advice or disposal. The existence of the committee, which has brought together the most important of the city and state agencies which handle in any capacity cases of mental disease and defect, has effected a co-operation of effort highly advantageous to the patient, and by virtue of Baltimore's size and relation to the State of Maryland,



should lead to results not so easily obtained in other larger centers of population.

One important phase of the work has been the examination of cases in police stations, penal and correctional institutions; and in this connection the work at the Friendly Inn should also be prominently mentioned. The police station cases have been referred to the committee by several wide-awake magistrates. I do not recall a single case, thus referred, that was not insane, feeble-minded or a habit case; the latter often in combination with some degree of mental defect. It is surprising to find how many of these cases are repeaters, having had numerous arrests and having served a number of short sentences in the almshouse, jail or house of correction. They are nearly always cases of dementia præcox, paresis, paranoid states, manic-depressive or feeble-mindedness, and are the tramps, beggars, alcoholics and petty offenders whose handling occupies a large portion of the work of the police.

There is no question that if all of these cases could be subjected to a medical and particularly a psychiatric examination and a permanent disposal effected in as many instances as possible, there would result a large saving to the city and state, particularly in the operation of the city police department.

A certain proportion of this group of cases belongs in other states and it is only through a psychiatric examination that the status of members of it is determined and deportation achieved. It is a matter of common knowledge that each year sees a large number of insane and feeble-minded offenders sentenced and serving in penal institutions, who should by every human right be cared for and treated in a suitable hospital. The time is not far distant when all such unfortunates will be subjected to a medical and psychiatric examination as soon as they come into the hands of the law, and not as now after they have served some time in a penal institution, if indeed they are examined at all. Aside from the humanitarian standpoint it certainly would be far cheaper for the state to take care of these cases in the proper way.

A large number of feeble-minded young women have come to the attention of the committee. Many of these also have been repeaters, the worst "problems" the social agencies have to deal with. Some of these have had from *one to five* illegitimate children. Owing to the lack of a suitable institution in Maryland, for such cases over 16, and to the unwillingness of the health wardens or average physicians to certify them as insane, they have been allowed to run at large, swelling

the ranks of repeaters, prostitutes, delinquents and petty criminals and adding to the crop of feeble-minded off-spring. A number of such cases have been committed to our present institutions, the word insane of the certificate being construed in a broad medico-sociological sense.

Every charity organization in its daily work comes in contact with cases which should have a psychiatric survey. Appreciating this, a large number of such individuals have been referred to the committee, and have been studied with a view to disposition and treatment. It is surprising how often a psychiatric examination will solve a social problem of long standing. One prominent charity worker on hearing the result of a Binet examination in a young girl exclaimed "that settles a doubt and disagreement of three years' standing in our society."

The societies handling young girls and boys cannot deal with their cases intelligently and with proper regard for their future and for eugenics without a psychiatric examination.

The office of the committee is located in the center of the city, in the same building with the state hospital offices. There a record of each case referred is typewritten and filed for future reference. Running notes kept on each case make it as up-to-date as possible; with the records are filed newspaper clippings, correspondence and all other matter concerning the patient. In the event a case goes to a hospital, an abstract of the case is forwarded to that institution, and if it is an after-care case, an abstract of the hospital record is received and filed with the committee's extra-mural record. Family and personal history of each case is made as complete as possible. It is believed that these records will eventually form a valuable index and record of the state's defectives, "cranks" and criminals as well as mental cases, and valuable data may be gleaned therefrom as to the nature of the city's problem in the handling of the vagrant, the moron, the delinquent and the criminal. Such work, it seems to me, forms an indispensable part of the civic administration. Such work is essentially constructive, and is an important avenue through which we can hope to effect a solution of a problem which is costing this and other states millions in money and more millions in loss of efficiency each year. The hospital is the mother unit, but the broad field of extra-mural psychiatry is where actual problems must be met and a solution effected.

## A STUDY OF THE BENIGN PSYCHOSES.

By AUGUST HOCH, M. D.,

*Director Psychiatric Institute of the State Hospitals.*

In non-mental diseases we attempt to describe the process in terms of chemical or tissue changes with the resultant disorders of function. In psychiatry we also have diseases in which the same principles are applicable, namely, the so-called organic psychoses. These are all characterized by intellectual defect symptoms. It would seem that in this group of cases we are dealing with primary chemical or tissue changes and

secondary defects in function. But there are also other mental disorders which seem to follow different laws, namely, the so-called constitutional disorders, such as hysteria, manic-depressive insanity, and dementia præcox. It is more probable that in these conditions we cannot in the same sense speak of primary and secondary events, physical and mental. The adaptations which we call mental have very likely two sides



to them, and it may be that we shall some time be able to describe every reaction of this sort from a mental and a physical aspect. But this is a promise of the far future, since we know next to nothing of the physical aspects of these reactions.

On the other hand, the researches of recent years have revealed many facts which would seem to permit us to obtain some insight into the play of even the deeper forces involved in mental processes, and to see some of the laws in the sequences of events which lead to abnormal outward disorders in mental adaptation.

Although we chose this realm for our field of work, this does not imply a denial of the existence of another aspect of the problem of constitutional disorders. We chose that side of the investigation which was accessible.

The attempts at understanding manic-depressive insanity have so far been guided chiefly by points of view which are applicable to the organic psychoses. Thus changes in blood supply, poisons, etc., have been made responsible. But these attempts have not gotten us beyond wholly unproven hypotheses. The desire, therefore, to understand this disease from the point of view of a dynamic psychology was natural, especially since considerable insight had been gained, in this way, into the nature of the neuroses.

I desire here to briefly report some studies on manic-depressive insanity which were carried on in collaboration with Dr. MacCurdy and Dr. Kirby.

Since these studies deal in part with Freudian psychology, it is indispensable to say a few words about this, more especially to mention some facts and some formulations which seem to me fairly safe, or at any rate useful for the study of psychiatry. In the first place, we must mention the existence of *unconscious motives*. Irrespective of any facts brought out by psychoanalysis, it is easiest to demonstrate these by the so-called post-hypnotic suggestion. We imply by this term the fact that we can experimentally create motives for action, which actions are later carried out without the motive entering consciousness. This is the first fundamental fact to keep in mind.

The second important fact is that Freud, for the first time, revealed to us a new world of such unconscious motives of which we had been practically ignorant. He insisted, in this connection, on the importance of early life, and pointed out that motives then created do not disappear but undergo a further development. On account of this further development they have in their original form stopped being a reality to the normal adult consciousness. On analysis, however, Freud found—to take up only one set—invariably unconscious motives which referred to the first attachment of the individual, *i. e.*, the attachment to the parents; more particularly did he find motives connected with great love for the parent of the opposite sex.

The possibility must *a priori* be admitted that such early attachments might play a rôle in the development of the adult love instinct. But the adult love contains sensual elements which are not present in the child and not contained in the

tender feelings toward the parents. As puberty approaches, these sensual feelings manifest themselves however. The great task of puberty seems to be the solution of the bonds of home and the transference of affection in part, together with the sensual feelings, to new objects, in the service of the instinct of propagation. This is not possible to every individual, and the assumption is made that in such cases the current of the sensual impulses flows then in the direction of the tender feelings, *i. e.*, toward the parent. Since there is, however, a strong opposition to this on the part of the conscious personality, this sexually intensified part of the attachment for the parent remains repressed and unconscious. We may say, therefore, that in the course of development certain steps did not take place. This arrest of development in the sphere of instinctive desires, which represent the very center of the personality, results in a defective adaptation, especially in the sexual sphere. When it is therefore stated that there is a sexual cause in every neurosis, this does not imply a sexual cause in the adult sense but in the sense that the cause lies in the imperfect instinct development.

The unconscious has different depths, as it were, and these infantile motives, which we have just mentioned, are undoubtedly among the deepest repressed strivings.

But now we must mention another point: In order to understand these infantile motives, we must free ourselves from our adult logical thinking and meet our patients on their infantile level. Most people, knowing that Freud has spoken of sexual causes and of the longing for the parent, simply combine and translate this into terms of adult sexuality. This is probably wrong, precisely because the formulation is too adult. The ideas expressed in the psychosis are often much more vague, expressing more a desire for some sort of possession. In the benign psychoses, in which we have chiefly studied women, this longing is often expressed in the wish to die with the father and the wish for removal of the mother. Let me briefly cite a case: A woman becomes neurotic when she gets engaged. After marriage she first refuses to submit to the marriage relation, and then develops a psychosis in which the ideas expressed are essentially that her marriage is annulled, her mother dead, and that she herself is following her father into his grave, is united with him in his coffin. In other words: She was unable to adapt herself to her married life, and regressed to a union with her father. This is not sexual in the adult sense, though it is an evidence of imperfect sexual adaptation that she could not comfortably fulfil her marriage obligations.

And here is another important point, namely, the thoroughly illogical nature of this, as of all other trends in such and similar psychoses. I will mention only one among many illogical features. On logical grounds it is absurd to wish—and we regard the delusions as expressions of unconscious wishes—that the mother should die, when all that is desired is to be united with the father in death. But the psychosis does not think logically but autistically, as Bleuler has expressed it. The wish for the mother's death or removal exists, because to the child she is the rival in the affections of the father. We must not forget that the ideas expressed in



psychoses are often, so far as we know, direct emanations of unconscious desires which cannot be understood by the observer or the patient when standards of logical thinking are applied to them. And, when we try to cast them into logical or adult forms, we are doing something which is, strictly speaking, not possible, and the formulation is apt to become one-sided and artificial. To recognize this is important. The vagueness of these trends is not due to our imperfect knowledge of them so much as to their very nature, and we are not improving matters if we make them clearer than they are.

It has been said that the infantile motives, upon which Freud lays so much stress, have been revealed by a method which is questionable, owing to the great latitude given in it to interpretation. But in studying the psychoses we find exactly the same motives as those which Freud has inferred, and here very often no complicated interpretation is needed, since the unconscious desires are expressed directly in the ideas of the patient. This is what should make the central claims of psychoanalysis so convincing to the psychiatrist. Freudian psychology, however, can be understood only when the dynamic importance of the deepest infantile motives is fully grasped, and this is a side on which even much of the psychoanalytic literature does not lay adequate stress, since it emphasizes more the method and the motives which are more closely related to our adult way of thinking. The psychoses, more than anything else, impress us, however, with the importance of the infantile motives.

In our study of manic-depressive insanity, we started from a review of atypical cases, and we found some important facts. In the first place, we were able to circumscribe certain hitherto insufficiently characterized clinical pictures which we respectively termed "states of perplexity," "states of coarse excitement" and "benign stupors." We also found not infrequently some interesting initial states which preceded the more typical psychoses. Then, again, the material itself, and points of view gained from other studies, urged upon us a careful consideration of the, otherwise neglected, content of these psychoses, *i. e.*, the ideas expressed by the patient, and we were more and more driven to a study of the relationship between the content and the emotional reaction. We then began to see certain laws in this relationship, *i. e.*, we found that certain types of content were typical for certain types of reactions. This, of course, refers to more than merely the well-known fact that depressive ideas occur with depressive, expansive ideas with expansive reactions; we also found certain typical contents in stupors and in states of perplexity, for example, and this led the way to the understanding of another principle of this relationship which will appear later, namely, the relationship between the reaction of emotion or conduct, and the level, infantile or adult, which was expressed in the content.

We may in the description of these studies begin, as we did in the work itself, with the stupors. Here we found in women strikingly often the idea of dying with the father and visions of the father beckoning. A similar content, even more elaborate, was noted in other benign psychoses to which it would

be difficult to give a descriptive name. We must have seen this content before, but it never impressed us as of any special significance. Now, however, with our knowledge of the infantile unconscious strivings which we had learned to regard as furnishing the most deep-seated motives in the interplay of adapted and non-adapted tendencies of the personality, we began to recognize in the appearance of these deep unconscious wishes important forces. Similar infantile motives, or immediate derivatives of them, were also found at times in the short initial states above mentioned. But, when a retarded depression, or, sometimes, when a manic state supervened, these infantile ideas disappeared, though they had been present before. It looked, therefore, as if a modifying influence was exerted, upon the ideas which are allowed to enter consciousness, by something which also determines the general reaction.

Since we desired to study particularly the depressions and elations, we next wished to know why, in depressions and elations, these infantile wishes disappear. We had studied, extensively, the precipitating causes of these conditions with results to be presently spoken of. In this study of precipitating causes, we came to a group of women on which, alone, I shall try to illustrate certain principles. These are women in whom the precipitating cause of a retarded depression was the death of the mother. The content of these depressions was quite superficial, and the death of the mother played no rôle in it. Further study of the content of retarded depressions showed us that this very superficial nature of the trend is the rule. It is, of course, natural enough, one might say, that a woman is sad when her mother dies, but it is not natural that she should develop a retarded depression, and it certainly is quite striking, and in need of explanation, that the idea of the mother's death should be wholly in the background of her thoughts, during the depression. An old experience, which had never been understood, then came to mind, namely, the character of the so-called reactive depressions. It will be remembered that in these depressions the sequence of events is as follows: Something happens which worries the patient, and the same thing continues to worry him so long as the depression lasts. But—and this is the interesting point—these depressions are not associated with retardation.

We argued, therefore, that in the retarded depressions, due to the death of the mother, the precipitating cause must act in a different way from the precipitating cause in the reactive depressions. Now, we knew the infantile unconscious motives, and we knew the fact that the idea of the mother's death often appears as a delusion, therefore as a wish, in other types of benign clinical pictures with different precipitating causes. Therefore we concluded that in these women who develop retarded depressions after the death of the mother, the psychosis is the result of the fulfilment of an unconscious wish.

We then found that this principle, namely, the principle that precipitating causes of psychoses act, not through their superficial, manifest meaning but through the significance



which they have for the unconscious wish life, we found, I say, that this is a wide-spread and important principle.

We then went back to our other experiences, namely, the fact that there are quite a number of cases in which infantile wishes actually come to the surface, and to the cases in which they are present and disappear when a retarded depression comes on, and we remembered the general conclusion at which we had arrived that a modifying influence seemed to be exerted upon the ideas which are allowed to enter consciousness by something which also determined the general reaction. The inference which we drew from all this and other facts, which it would take too long to enter upon now, can then no longer be called far-fetched: We concluded that one of the chief functions of retarded depressions must be that of *repression*, or that the purpose of the depressive retarded reaction is to repress the infantile unconscious strivings.

In the above-mentioned group of cases, which follow the death of the mother, we may say that the infantile unconscious strivings became inflated on account of the fulfilment of an unconscious wish, and the function of the depression is then to repress these unconscious infantile desires. But the infantile unconscious strivings may also be inflated in other ways. It is well known that when, for some reason or other, satisfaction is not obtained in life, there is a tendency to that which Freud has called regression to earlier types of satisfaction. This may happen when suddenly an important source of satisfaction is taken out of the life of an individual—it may also happen when a demand is made upon the person which he or she cannot fulfil. The above-cited case of the woman who could not adapt herself to her married life, and developed a psychosis with the content of dying with her father, illustrates this well.

Enough then: we found that what the precipitating causes do, is to inflate the infantile unconscious desires. We might then describe the sequence of events which occur in depressions, as follows: We have an individual who is constitutionally predisposed. This predisposition shows itself, as we have found, in frequent mood alterations—the patients present a depressive or a hypomanic, or a cyclic make-up. This probably has to be interpreted in the same way as the psychosis itself, namely, as a defect of development on account of which the deep unconscious wishes are more easily stirred than in normal persons. Then the precipitating cause, or a series of causes, inflate the deep unconscious desires. The next result may be that the unconscious wishes come into consciousness, as in some of the other benign reactions, or in short initial phases, or sometimes merely in dreams. But in depressions, though they may be preceded by such clinical pictures, it happens more often that the infantile desires are, from the start, repressed. Depression, therefore, is not merely sadness or something akin to hunger, an unsatisfied desire, not further reducible, although this is probably an element in it; but retarded depression is, above all, a protective attempt on the part of the personality against the destructive unconscious forces; an attempt which is successful. This repressive function may also explain the great lowering of energy and initiative, since

it might be assumed that the energy is expended in the great task of repression, although this formulation is of course as yet only tentative.

Such protective mechanisms in the interplay of forces are well known in general pathology, and we are, therefore, not introducing a new principle, foreign to our medical thinking. There are evidently different forces in our mind, destructive and conservative ones. The former are the purely non-adapted egotistic tendencies of the deep unconscious; the latter, the more adapted social tendencies which I have called the main tendencies of the adult personality. And it seems that in manic-depressive insanity, *i. e.*, in the benign psychoses, it is the conservative forces which have the upper hand. This in turn would seem to account for their benignity.

In the work on the manic states, we started our study with the precipitating causes, and we found that they represented essentially fulfilments of unconscious wishes. But we had found this also in some cases of depressions. The difference became clear only after we had studied the content of manic states more fully. We found chiefly two types: a religious one, and an erotic one (ideas of having lovers, etc.). Other contents were more difficult to understand but, as we later found, did not differ in the essential characteristics. What are these essential characteristics? It was about the same time that we studied the content of manic states of dementia præcox. These states differ from the benign manic states in certain formal aspects. But a more striking difference was found in the content. In the dementia præcox elations, we found plain infantile material, as, for example, in the case who thought her father had put a bean or a seed into her rectum, and that she was pregnant. Such or other infantile material we found to be invariably absent in pure benign manic states. We concluded from this, and found it to be a general principle, that what characterized the content of the benign manic states was their adult level. In other words, while we have seen that infantile desires of a certain type may appear in some forms of benign psychoses, they are never seen in depressions, but are there repressed, while superficial ideas are substituted; in manic states they are also absent, but what has to be regarded, probably, as adult sublimated derivatives are permitted to enter consciousness. Now, the question as to the difference in the precipitating causes received a new impetus, and it seems probable that when depressions are produced by precipitating causes which represent a fulfilment of an unconscious wish, this is always on an infantile level; whereas, the wish fulfilments contained in the precipitating causes of manic attacks are on an adult level. This means that the precipitating causes of manic attacks furnish a situation which points the way to an autistic adult outlet, an outlet also for unconscious wishes, but these wishes are not on an infantile level. So much seems clear. But, among other reasons, the very fact that, just as in the case of depression, we find patients who presented ideas of an infantile nature which disappear as soon as the clinical picture assumes the character of the manic reaction, suggests that even in the precipitating situations of



manic attacks elements must be contained which, as we expressed it above, inflate the infantile unconscious desires. This is not fully worked out. But there are a number of facts which point that way. It would take too long to give and discuss the evidence.

This very compressed, incomplete, and somewhat schematic

account of our work on manic-depressive insanity will have to suffice. I hope to have been able to show that new points of view have been gained which throw some light upon the psychological meaning of this difficult disease. In every direction, however, new problems and unsolved questions loom up, to which much further work has to be devoted.

## ETHICAL ASPECTS OF PSYCHOANALYSIS.

By JOHN T. MACCURDY, M. D.,  
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Psychoanalysis in this age, when most methods of scientific study are hailed with joy and adopted often with more enthusiasm than their promise justifies, stands in a peculiar position. On the one hand, its school has probably gained more adherents from the ranks of sober, serious investigators, in its short career of public existence, than has any other mode of mental healing; it has already its mountebanks and its notoriety. On the other hand, those who are not for it are not neutral but are against it and oppose it with a bitterness more in keeping with a theological than a scientific polemic. They charge the psychoanalysts with forming a cult, which parades in public with a propaganda of pseudo-science based on "personal experience" but which preaches an orgiastic religion in private.

This is a singularly favorable opportunity to discuss how it comes about that what ought to be a matter for dispassionate observation and reasoning has become the signal for bitterness and innuendo. This gathering celebrates the foundation of the first medical school in this country, devoted to investigation as opposed to empiricism. We, its alumni, have a stronger voice in the scientific community than the sons and daughters of any other school. Our responsibility is, therefore, the more urgent, that we should, as occasion arises, be prepared to further or oppose the spread of this movement. Its teachings are true or they are false; our attitude cannot change that. But there is no clause in the oath of Hippocrates or the charter of Johns Hopkins University which encourages neutrality.

To use a psychiatric term, this celebration is the precipitating cause of this paper, but the choice of subject is largely determined by a less accidental circumstance. As many of you know, the ranks of psychoanalysts have lately been divided: Jung and the Zürich school have broken away from Vienna and Freud. This is no time to discuss the points at issue; though fundamental, they are academic; but it is of great importance to note that the keystone of the Freudian theory has been rejected by Jung, and that this keystone is the target for the abuse of the opponents of psychoanalysis in general. If a theory comes to be the watchword of loyalty, produces a rebellion in the camp and, at the same time, is the original cause of the war, it must be fraught with meaning for the emotional as well as the intellectual life. This theory is that sexual instinct is a basic, dynamic mental factor, particularly in its abnormal tendencies; that it operates in the

unconscious, and that its roots are in infancy. The "religion of healthy-mindedness," as William James has termed it, has largely done away with the doctrine of original sin. Now it returns in a jargon of "complexes," "repressions," and "sublimations." Is it any wonder that this teaching should be opposed with more emotion than logic, that it should be called a "pest"; its publication placed on a German scientific *Index purgatorius*, and its followers in many parts of Europe exposed to ostracism?

The bitterest opponents of psychoanalysis are those psychiatrists who see in mental abnormalities not a disturbance of function but an organic change in the brain. Imbued with the materialistic spirit of the age, they restrict science to what can be weighed in a balance or seen with the eye. That the observation of phenomena which are capable of experimental production constitutes a science, they will not admit, unless these phenomena can be translated into physical or chemical terms. Considering the trifling degree of correlation as yet established between structural alteration and brain function, these investigators are in the position of men so convinced that all water comes from the clouds that they will not think of damming a river in a flood. But why should these Laputa philosophers object to others working with the material at hand? The meteorologist is not jealous of the activities of the irrigation engineer.

To answer this we must turn for a moment to consider what the attitude of the world has been toward scientific research. Ever since man has begun to speculate, he has been asking the question "Why?" and he has always found an answer. It has been magic, animism, demonology, pantheism, polytheism or theism. But amongst men have always been those who have also asked "How?" They were the Galileos, Pasteurs and Darwins of their age, and their discoveries have always forced the "Why" to a still more ultimate cause. Their claims were always regarded as blasphemy and, consequently, they suffered appropriate persecution. But now a curious change has taken place. The question has not been answered; but so many of its formulations have been settled by an answer to "How," that the unthinking world has concluded it is safe to trust to that agency for the answer to "Why." Belief in a physical or biological theory is the modern creed. A few centuries ago the alchemists sought salvation by working with metals, which represented the attributes of man and the Deity. On the modern Olympus sit the electron, the



amboceptor and the colloid solution; have faith in them and your grandchildren will enjoy the fruits of the flesh forever!

We can now see why psychoanalysis is heresy and should be rooted out. It flouts these gods with the statement that an idea may be of more importance to a man than the presence, absence or separation of a few axones and dendrites. Still worse, it insists that these pathogenic ideas are not known to the victim himself. What an affront this is to the creed of Goll, Wernicke and Broca!

But the mere existence of a bigoted opposition to psychoanalysis is no proof of the validity of its claims, nor is the opposition confined to the so-called "organic" neurologists and psychiatrists. The men in France and America who have been doing faithful psychological work with the abnormal for the past two decades are, many of them, almost equally antagonistic. This antagonism may account for a refusal to make an honest examination of psychoanalytic claims. But what are the objective proofs that those claims are sound? The method of analysis is free association, and all those who have faithfully worked with it are convinced that its results are not to be accredited to suggestion to the patient. But this is indubitably "personal experience." Free association can be obtained only when the patient and examiner are isolated; the presence of a third party, who should judge of the genuineness of the proceeding, would be fatal. At the same time results are obtained only when the analyser is keen to follow any clue presented in a passing phrase, a slip of the tongue, or a peculiar action. He must seize on this and force the patient to continue to associate without evasion until the under-lying thought is relentlessly brought to expression. Now it is obvious, that, be he ever so conscientious, no man can begin with a feeling of scepticism and recognize the slightly anomalous reaction. Consider the differing interpretations which honest men of opposing parties give to the actions of a politician. Is it therefore surprising that we hear men of equally undoubted scientific probity affirm and deny the results of the method of free association? We must admit that, though its results carry conviction to the minds of the Freudians, it cannot be admitted as a flawless objective proof. But what of the cures; the reports of chronic sufferers who have finally been rid of their symptoms and given a mental poise only after psychoanalytic treatment? Unfortunately this argument, too, is not final. Kings and saints in times past have laid their hands on sufferers and accomplished similar results; Christian Science, New Thought and a score of mushroom cults can point to analogous results. True it may be that the patient cured by psychoanalysis has not substituted for his symptoms the belief in some superstition that puts a strain on his critical faculty; but, after all, what does society care for that? The patients were sick and dispirited; now they are well, happy and energetic. It will take a generation of statistics to show that psychoanalysis produces more permanent results; and, in the meantime, we are not justified in assuming that a pragmatic is a scientific value.

If there were no further evidence to be offered, we could pardon the opponents of psychoanalysis with a regret that

their prejudices were able to conquer their zeal for impartial inquiry. It is only presumptive evidence of its specificity that a certain bacterium is always found in a certain disease. The organism must be able to produce the same symptoms experimentally. Similarly, if we can find the principles of psychoanalysis demonstrated in other situations than in the neuroses, and if they come to light without the aid of any special method which is open to criticism, then we can say that the claims are proved and that opposition implies wilful ignorance.

Psychoanalysis claims that the unconscious wish gets its gratification through a symbolic outlet. Certain symbols constantly recur with the same latent meaning—why we do not know. Now it is found that, if we turn to comparative mythology and folklore, the symbols of the neurotic's dreams form the basis of myths, superstitions and primitive customs. Then if we translate the manifest form of the myth or ritual into its latent meaning, as derived by analysis of the neurotic symbol, we make an extraordinary discovery. A few themes are the basis of all myths and customs, no matter what age or climate has produced them! More than that; the early myth of a cultured people represents the same degree of distortion and disguise as does the contemporary production of the savage or the naive expression of a child. The conclusion is obvious that these wishes are universal; that the consciousness of the child or the savage corresponds to the unconscious of the adult civilized man; and that, therefore, the process of disguising the infantile wish proceeds similarly with the child or with the race. This corresponds in the sphere of psychology to the teaching of biology in the sphere of morphology, and is, therefore, a cogent argument in favor of the validity of psychoanalytic claims.

But we have here made an assumption which a hostile critic might not allow and so again we shall admit that the proof is not final. There is, however, another field where the truth of psychoanalytic claims is so easily established that, once traversed, one wonders that psychoanalysis had not its origin there. I refer to the field of psychiatry. Once guided by Meyer and Freud to the point of viewing the content of a psychosis as worthy of study, we make an almost staggering discovery. The insane, particularly dementia præcox patients, give thinly veiled or often perfectly bald expression to ideas that are precisely what Freud and his pupils have claimed to be the pathogenic, unconscious wishes. In fact, the identity is so manifest that it often seems as if the patient must have read some treatise on psychoanalysis. Indeed several sceptics, confronted with this evidence, have asked me if that were not the case, little knowing that the patient was an illiterate pauper. The genuineness of these productions is so convincing that we are sometimes confronted with the only remaining objection—hardly a scientific argument: "Well, after all, they are crazy people." True; but if this criticism has any meaning it is in its implication that the talk of the insane person is like a heap of refuse in which almost anything may be found, so why not Freudian "complexes"? If so, there can be no why and wherefore as to what particular ideas are ex-



pressed. But the contrary is true. In the manic-depressive group especially, we are now often able, being given the make-up and the precipitating cause of a psychosis, to give an accurate prediction of the delusions to be voiced and the mood accompanying them—elation, depression, anxiety, etc. More than that, when we hear the delusions, we can often give a diagnosis without ever knowing what formal aspect the patient exhibits; or, what is of greater value, give an accurate prognosis on the basis of the trend when the formal aspects are equivocal. We can now sometimes formulate what the older psychiatrists “felt” as reasons for or against a good prognosis. If, while we are still only at the beginning of our investigations, we can put psychoanalysis to this objective, experimental proof, there can be no evasion with a sneer as to the material being “crazy.” We are now able to state unqualifiedly that the human mind does work as Freud claims; that a great dynamic factor is the unconscious wish, whose content is the desire for satisfaction of an infantile type of sexuality. These statements are no longer theories; they are objective facts which no psychiatrist, at least, can be scientifically honest and deny.

But why affirm? We know where our beef and fertilizer come from. Should we, therefore, have an abattoir next door? Should we demand that every surgeon be a proctologist? This is the most serious objection of all, because it springs from emotional rather than logical thinking; in fact psychoanalysis offends the taste of its opponents much more than it does their critical faculty. To believe in the unconscious is no greater strain on credulity than to believe in the existence of a filterable virus, which we know only by its effects. If psychoanalysis be what its enemies think it, I agree that they have a right to leave it alone; one ought to be able to eat meat and wear shoes without first visiting the abattoir. This, however, is not the real psychoanalysis. Its literature is not pornography; it does not degrade humanity. That is the same error which made people cry out that Darwin claimed all men were monkeys. Man's lineage may be traced back to some primordial ooze without his losing his dignity as man. Perfume as such smells no less sweet because a chemist can split it up into a number of stinking liquors. Rather do we honor him when he synthesizes those liquors into the perfume and transforms the stench into an entrancing odor. Now he who examines the philosophy of psychoanalysis, sees that man has built and nourished his culture with his most animal and selfish instincts. He has been his own chemist. Are we, therefore, to abhor or honor him? If the rosebud gets its beauty from roots bedded in a mass of carrion, should we despise it, or admire the miracle of nature?

This analogy is close and yet the situation does not seem so clear to those who are not conversant with psychoanalysis and, moreover, thoroughly conversant with it. The explanation of this blindness lies, I think, in the failure of the beginner to realize two things: First, that the unconscious is *not* the conscious mind; and second, that outlet to an unconscious wish in the channel of a sublimation is a vastly different thing from a direct outlet. These are the ethical aspects of psychoanalysis.

There is comparatively little opposition to believing in the existence of unconscious mental processes such as are evidenced by automatic actions. These can be produced experimentally by hypnosis, and it is generally agreed that all automatic acts are determined unconsciously. Psychoanalysis, however, meets with the first serious resistance when it claims that the act is determined by an unconscious *wish*, and the resistance becomes open hostility when it is stated that these wishes are repugnant to the personality of the subject; that their fulfillment implies immorality. The opponents say this is an insult to humanity at large and a libel on the individual. Strictly speaking, however, are we right in ever calling a thought immoral? Should we not confine that opprobrious term to the act which may result from the thought? If thoughts can be immoral, then he who is tempted has already fallen. To take a banal example: a pauper passes a fruit stand, looks hungrily at the fruit but decides not to steal it. Is he wicked because tempted? Moral or immoral, however, these thoughts are dangerous; the man into whose consciousness they come is more apt to commit the act of folly than he whose consciousness is free from forbidden wishes. Suppose now that our pauper succeeds in stifling his desire to steal the fruit till the sight of it no longer makes him consider stealing, but yet his mouth waters when he sees it. We now admire him the more since he has made himself incapable of temptation. But what do we see if we analyse the situation? His mouth waters; therefore, consciously or unconsciously he must imagine that food is in his mouth. He is certainly unconscious of his having taken the fruit and put it to his mouth in imagination. Now whatever view we may hold as to the morality or immorality of being under temptation, the unconscious thoughts in this case can certainly not be judged by any ethical standard whatever. The mere taking of food and putting it in one's mouth is obviously nothing but a physiological necessity; and the sight of food in this case has produced a physiological reaction, which has no moral relation to the actual situation. Had the hallucinated unconscious links in the chain been conscious, the case would have had its ethical aspects for the wish (of itself innocuous) would then have had its fulfillment in a real situation and involved the crime of theft. In a word the unconscious wish has no moral handle to it, for, being out of consciousness, it can have no relation to any actual situation and, therefore, by no chance whatever lead to any crime. To hold one morally responsible for his unconscious wishes is as ridiculous as to chide him for harboring a parasite which eats his dinner and makes him continually hungry.

But, it may be urged, the unconscious part of this example deals with a normal act, the abnormal part is merely implied; whereas, according to psychoanalysis the unconscious wishes are of their very nature evil. To answer this one must examine the history of these wishes. To discuss them all would demand a lengthy treatise, but one alone will serve as a sufficient example, since it is the most fundamental of all. I refer to what is usually termed the Oedipus complex; that is, incestuous attachment to the parent of the opposite sex. The infant during his first years has a love for his mother expressed in a feeling of tenderness and gaining as complete a physical outlet



in mutual caresses as his body is capable of. Soon, however, dim glimmerings of sex consciousness appear, and probably at about the same time his ethical feeling begins to grow. A struggle ensues in which the sex feeling is repressed, taking up its abode in the new-born unconscious. As fast then as the idea of any further outlet dawns on him, it becomes an unconscious wish. At no time, therefore, can we say that these wishes have been in consciousness and confronted with a real situation that gave a chance for complete outlet, as long before puberty, not only the incestuous wishes themselves, but everything connected closely with them have been relegated to the limbo of the unconscious. All that is legitimate in the way of tenderness can remain conscious, but so soon as the desire of the child for possession of the parent passes that boundary it is repressed. That it is in the unconscious is a tribute to the morality of the individual. But, it may be asked, what right have we to call these infantile longings sexual, and if larval, why is the adult unconscious wish so plainly sexual? The first question is equivalent to the charge against Freud that he has enlarged the meaning of that term sexual. As a matter of fact, all he has done is to be logical with it. We are accustomed to call the same phenomena by different names whenever consistency is embarrassing. But if a man were to treat a strange woman with the freedom and tenderness he shows to his mother, would anyone hesitate to call his behavior erotic? The second question is answered as simply. Physical indulgence past the degree of infantile tenderness is a vague thing to the child, who could not formulate it if he tried. But the adult can. For him it is a definitely sexual act. When we say then that the unconscious harbors incestuous wishes, we are using a kind of shorthand. What we really mean is: there is a desire for possession of the parent so strong that it cannot be put into adult language except in sexual terms.

The fact of the unconscious existing is, therefore, a proof of the moral strength of the individual on the inhibitive side. Repression keeps him from doing evil. But what has psychoanalysis to say about the positive side of morality? This leads us to the question of sublimations.

When repressed these wishes are not suppressed; they are merely refused admission to consciousness in their absolute nakedness. They reappear in various disguises, that is, as symbols. In every-day life these symbols are, generally speaking, symptoms and sublimations. Biology teaches that there are two great instincts, that of self-preservation, and that of the preservation of the species. We can also term them selfish or individualistic and social instincts. All permanently unconscious wishes are individualistic; sublimations consist in the union of social and individualistic aims. A man may build tunnels through "Mother earth"; a woman may do religious work in the service of her "Divine Father"; the examples are endless. In every case the activity represents symbolically the indulgence of the unconscious in a way to escape censorship and, at the same time, benefits mankind. The fact that the selfish, unconscious component is essential is really well known to every one. We all know that no one

succeeds in his task when his heart is not in his work; as we say. In other words, his occupation must satisfy some inner, personal craving. That nature has regulated this automatically is shown in the psychoses, as Dr. Hoch has just told you. We cannot work well when sad; we never are so effective as when happy. In the psychoses we see depression when the unconscious wish tends toward plain expression. When it takes the form of a sublimation, elation results. Occasionally, too, we see the same wish coming to expression in different delusional forms, finally assume that of an effective sublimation, bringing the patient back to reality and sanity, and after recovery providing an outlet which the sufferer never had before the attack. Now, is not this a tribute to the human psyche? What a loss it would be if all our repressed instincts were mere lost energy. We now see that they provide the motive power for those activities which benefit our fellow men.

Finally a word as to the value of the knowledge of psychoanalytic principles to the individual and the community. In the first place they force us to honesty of thought. No one can successfully analyse another who does not *pari passu* analyse himself, for if he be struggling against some unconscious tendency himself, he is not liable to recognize the transient suggestions of its operations in others. He learns, therefore, to examine his own opinions and attitudes. If he finds that he holds some view more strongly than his neighbors, he realizes that it must have some vital unconscious significance; this attitude once gained, he is free to examine it objectively. No one who knows that all our activities represent conscious or an unconscious self-indulgence, can shield his conscience with the plea that his action has an altruistic motive. He must look beneath the surface and see toward what result his action tends. For example, the parent who spoils his child is convinced that he is sparing it pain when he withholds discipline. This is true, but his real motive is a selfish one; he is avoiding the pain it causes him to see one suffer whom he loves. Let him but realize that, and he is prepared so to treat his child as to spare it as much life-long suffering as education can protect it from, irrespective of what temporary sorrow discipline may bring.

Secondly, psychoanalysis gives us not an infallible but a general method of gauging the sanity of conventions and laws. The analyst knows two things: First, that an extravagant effort at repression denotes an unusually strong unconscious tendency, for instance, that prudery implies a crude unconscious immodesty; second, that repression finds its expression in laws and customs before it is an integral part of the individual's life. As an example of this, we may mention the elaborate systems of tabu and exogamy among primitive peoples which are directed against incest. With us such tendencies are so soon relegated to the unconscious that incest is, relatively speaking, an unknown crime. Many of our conventions are as ridiculous as tabu, though not so extensive. The analyst sees in conventions and laws the effort of society to protect itself; but, because he sees plainly that against which they are directed, he can also see their extravagances. He remembers that, though their general purpose is good, their



form is artificial and that each generation is dominated by the customs of those preceding. Tabu makes family and industrial life, as we know it, impossible. Think of the pass we have come to in America, from our prudery, with our white slave traffic and our inconsistent divorce laws! When a knowledge of psychoanalytic principles has become general, our laws will correspond to the moral sentiment of the community. They will be laws that can be enforced, as they will represent the aspiration of the community rather than the extravagant, hysterical repressions of the law-makers, who satisfy their consciences by making illegal what they most want.

Let us sum up this critique of psychoanalysis. We have seen that certain of its features have aroused antagonism without and caused dissension among its disciples. These teachings are seen, when critically examined, to be true, and we have accounted for their non-acceptance by their exciting

an emotional hostility. This emotion is due, we think, to the fact that psychoanalytic doctrines arouse moral repugnance, a fact which forces us to see whether the ethical aspects of this new science are good or bad. We find that when rightly viewed these theories teach us that man has an inherent morality stronger than we suspected, and that he has succeeded in transforming his lowest, most selfish tendencies into work for the betterment of his kind. Finally we see in psychoanalysis the promise of a more honest form of thinking, not only in the individual, but also in the community. Its very basis, therefore, is ethical; an emotional misconception accounts for the opposition it has earned. Psychoanalysis is a new science; some of its formulations may be temporary; the conclusions of some of its adherents may be hasty and crude, and, in so far as they are crude, incorrect. But as to its basic concepts, we feel confident in saying that, rightly understood, they can have no opponents.

## OBSERVATIONS ON EMBRYO GUINEA-PIGS.

By STEWART PATON, M. D.,

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The interest and sympathetic welcome with which reports upon the study of the nervous system in the lower animals are received, in institutions devoted to the investigation of the activities of human beings, is a fact that deserves consideration from those who are interested in the development of the biological sciences. A very long road has been travelled before this much desired consummation has been attained. Gradually we have come to recognize the importance of uniformity, and the unbroken character of the chain of activities that begins with those of the lowest organisms and includes the conscious processes of man. In the relatively simple reactions of amoeba or medusa, phenomena are often observed which give a clue to the nature of the mechanisms concerned in the complicated cerebral processes of the higher vertebrates.

In addition to the phylogenetic approach to the study of the complex activities of the brain these problems may, with certain decided advantages to the investigator, be attacked from the ontogenetic point of view. The various stages of development are to a certain extent under control or at least may be modified by the conditions imposed by the investigator. This experimental method facilitates the effort to bring the structural and functional changes taking place in the nervous system during the early life of the individual into more direct correlation. In a series of papers we have attempted to direct attention to the importance of this particular field of investigation.<sup>1</sup>

Although the questions relating to the correlation of structure and function in the nervous system are often discussed in terms that suggest the possession of considerable knowledge,

a careful analysis of the available facts does not always justify positiveness of statement in discussion. Unfortunately the natural difficulties of investigation in this particular field are considerably increased by the necessity of stopping to discuss the meaning and applicability of terms. My chief object in presenting this subject at present is to emphasize the desirability of giving greater latitude and more flexibility to terms in general use. In observing the development of the primitive movements of the vertebrate embryo the investigator is impressed with the synthesis of activities that is constantly in progress. One phase of development passes on into a succeeding stage without interruption. There are no points at which divisions other than those arbitrarily determined by the observer can be created. Although the artificial limitations imposed by the use of terms is often apparent in connection with the study of the higher activities such as consciousness, there is a tendency to describe the responses taking place in the lower planes in a very dogmatic form of phraseology.

Consciousness is merely a convenient word to designate phenomena occurring at certain levels and if the word is dropped from our scientific vocabulary it is not improbable that the reasons advanced for its rejection may be successfully used to discredit "habit," "instinct," "reflex" and many other words that serve a very useful purpose.

An excellent example of the arbitrary use of words may be observed in connection with the terms employed to designate the mechanisms associated with the lower planes of activity. If we carefully study the various phenomena occurring in connection with the development of the sucking instinct we cannot fail to be impressed with the difficulties created by any attempt to define in categorical terms, "habit" and "instinct." The mechanisms concerned in both phenomena are so intimately united that only an arbitrary distinction may

<sup>1</sup> The Correlation of Structure and Function in the Development of the Nervous System. Proc. Amer. Philos. Soc., Vol. I, II, No. 211, Sept., Oct., 1913.



be drawn. In the guinea-pig, this entire mechanism seems to begin with the responses obtainable by electric stimulation from that portion of the facial nerve that supplies the muscles about the eye. These reactions are followed by movements of the jaw, still later by those of the tongue and last of all by the muscular adjustments by which the head is turned from side to side or up and down. No sharp distinction should be drawn between "habit" and "instinct" in describing the synthesis of this complex mechanism. Whenever these two words are used to designate different links in the chain of the activities we create an arbitrary and unscientific division in order to facilitate description, and are at once open to the criticism that is aimed at those who are injudicious in their use of "consciousness." The fact that all these terms have decided limitations does not make it necessary for us to reject them entirely.

In the retreat from the camp of the metaphysician to the secure bases established in the laboratory and clinic there does not seem to be any reason for abandoning such very useful terms as "consciousness," "habit," "instinct" and others that could be mentioned. The retreat, if conducted in good order, will be much more to the credit of the investigator than if he is frightened by the bogie of speculation into a frame of mind that sanctions an effort to throw away useful terms.

From the study of adjustments taking place in the lower organisms excellent reasons are suggested for the retention of the word consciousness in our vocabulary; at the same time that emphasis is placed upon the unbroken continuity of that long line of activities which begins with the lower organisms and includes the higher mental functions of man.

## THE ONSET OF GENERAL PARALYSIS.

By CHARLES RICKSHER, M. D.,

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The important place which general paralysis occupies in the group of organic mental disorders, the fact that its onset is at the most active and valuable period of the patient's career, and the dire results which often follow its non-recognition, warrant a more extended study of the early symptoms than has heretofore been given to them. The finding of the *Treponema pallidum* in the brain, and the almost universal finding of positive Wassermann reactions in the blood serum prove conclusively that it is one form of syphilis which, if discovered before gross organic changes in the nerve cells and fibers have occurred, may react to treatment. Treatment in the later stages, or even soon after the patient has been sent to a hospital on account of mental disturbances, has not as yet produced the results which the therapists desire.

The clinical manifestations of the disorder depend entirely upon the intoxication produced by the action of the spirochæte and upon the damage done to the cerebral cortex. Since the trouble may be localized to certain areas or even to one hemisphere the clinical picture must differ greatly in various individuals and the sequence of appearance of symptoms vary according to the location of the lesion and the resistance of the individual, and possibly also to the intensity of the toxins which are produced by the causal organism.

It is extremely probable that some sensory and motor symptoms are developed in the majority of cases before mental symptoms are observed. Knapp<sup>1</sup> in his study of early symptoms of paresis found headache, pain in the legs and elsewhere, numbness and hypesthesia present in half of the early cases and in 68 per cent of the cases on examination. Eye muscle troubles occurred in one-third of the cases, and tre-

mors, paresis and ataxia were found in almost nine-tenths of all cases examined. Pupillary disturbances, unequal pupils, sluggish or absent reaction to light, were less constant than changes in the knee-jerk which were almost universally present, but they were found in over half of the cases. Mental symptoms, especially memory defects, nervousness and irritability were complained of by the patients in half of the cases, but on examination practically the whole number showed some mental defect.

Whether the physical or mental symptoms are more prominent in the early stages depends upon the accuracy of the early observations which are usually made by some members of the family, and consequently the stress laid on them varies greatly. Few patients with general paralysis consult a specialist in mental disease until brought by some of his friends. The anamnesis given at this time usually omits reference to any slight motor or sensory disturbances which may have been present for months, but were not considered of sufficient importance or severity to cause them to be mentioned.

The slight paresthesias, tremor of the facial muscles, a slurring or dropping of words or syllables in conversation or even slight changes in writing occur even in normal individuals at times, and unless one calls attention to them few consider them of sufficient importance to mention. Just as on the mental side, judgment defects are so commonly met with in all walks of life that few will give more than a slight passing attention to them unless they lead to some great expenditure of money or to some unusual act. Occasionally writing defects are noticed early, especially in those who write a great deal, as bank-clerks and merchants. I can recall one case of a merchant whose signature was changed so much that the bank refused to cash his check, although his family and friends had not noticed any marked change in him otherwise.

<sup>1</sup> Knapp, *Journal of Nervous and Mental Disease*, Vol. 35, p. 513, 1911.



Several attempts to group the symptoms of onset into types for clinical convenience have been made, notably by Bianchi,<sup>2</sup> who gives four principal modes of onset, but also notes that this disorder may begin with other symptoms. Bianchi's four types are: First, onset with exaltation of the mental activities, judgment defects, motor restlessness and activity, slightly grandiose ideas, expansiveness and generosity. There is generally a more or less marked loss of moral sentiment, of shame and of the sense of decency, and to all this is added very early, sometimes even before these changes are noted, loss of memory.

The second variety is characterized by progressive depression of all the mental faculties. The aptitude for work is diminished, there is a feeling of fatigue, attention is weaker, the powers of comprehension and judgment are diminished, new acquisitions are difficult and those previously acquired are lost. There is no intellectual and affective function that is not overturned in this decline and fall of the personality. The loss of memory is marked and the patient becomes dull and stupid.

In the third group somatic symptoms predominate, headaches, neuralgias and sometimes ophthalmic hemicrania long precede the illness. The most frequent and characteristic symptom is defect of expression of thought whether by speech or writing. There are partial and temporary pareses or paralyzes of certain muscles, especially in the apparatus of phonation, respiration and articulation. The speech and writing are slower than usual and grammatical errors are early seen. Impotence often precedes the disease for two, three or five years.

In the fourth group the individuals have always enjoyed good health. There is vertigo, fleeting confusion, sometimes headache. In other cases there is an unwonted affective excitability, irascibility, an inner restlessness and an inexplicable discontent, which precede for weeks or months an apoplectiform or epileptiform attack. When the attack is over there remains a restriction of the intellectual and affective fields. After several months or even a year the attack is repeated, generally with increased intensity.

Naturally, on account of the varying location of the lesion and the various personalities affected, we cannot group all the modes of onset into four small classes. Each case differs from every other case and the progress of the symptoms must differ according to the intensity of the infective organism and to the resistance of the individual.

As in the other psychoses, the make-up of the individual is of great importance in considering which symptoms will appear strongly marked and which will be considered as of moment by the patient or his friends. The physical disorders will be more noticed by a man who is living an active out-door existence, while the same trouble would hardly disturb an individual who is leading a sedentary or confined life and who is more or less subject to headache and gastrointestinal disorders. In the former case slight memory defects or

defects in writing or speech would pass unnoticed, while in the latter individual they would seriously interfere with his work and cause more or less trouble. In certain individuals one finds a distinct hypochondriacal tendency which is marked even in normal life, and in such cases the physical disorders would probably be noticed more early than in other men. Thus in determining the early symptoms one must also study the man in his normal state and form a picture of his personality in order to arrive at any conclusions as to which symptoms one would expect to find emphasized and which ones would probably be forgotten.

In the cases in which the physical signs are present, where there is more or less marked pupillary change, or speech or writing defect, the diagnosis is comparatively easy. The physical signs suggest paresis and a lumbar puncture will corroborate this diagnosis. There is a group of cases, however, in which physical signs are very slight or absent and the mental picture does not resemble that which one usually sees in paresis. In such a case frequent, careful examinations are necessary and every hint of any physical sign must be closely followed up.

The two following cases are good examples of this type of onset, the real diagnosis being reached only after the disorder had progressed for some time:

CASE I.—I. B. M.:

*Family History.*—Father died, aged about 66, of some form of paralysis. One nephew is said to be feeble-minded. One brother alcoholic.

*Personal History.*—Born in Pennsylvania, Sept. 16, 1869. Schooling was meager until he was about 18 or 20, since when he has attended school continuously either as a student or teacher.

He was of a kind disposition, at times irritable and impatient, very fond of a few friends but not fond of society in general, reticent, a very hard and continuous worker, but had never acquired the ability to rest from his work.

He came to Chicago in 1891, graduated from the normal school in 1892 and has taught since, in the University of Chicago and in various public and private schools.

He married in 1904, his wife dying five months later. He married again in 1906 and has four children.

He was temperate, his associates were good and he provided well for his family.

*Present Illness.*—In the latter part of October, 1911, he seemed to tire easily and was exhausted after a day's work. A week or so later he suddenly became depressed and despondent because he realized that he could not teach and was afraid he would not be able to support his family. About that time he won a lawsuit pertaining to the will of his father-in-law which meant a great deal to him financially, and also vindicated his character, yet it made no impression on him. He had no interest in his closest friends and would say, "I am all in, I've turned yellow." He went to Montana and lived in the open for a month. He did not write to anyone while on his trip and carried a revolver. He has often spoken of this as being his period of suicidal mania. His friends discovered him strolling around listlessly in a small town and sent him home. The condition of apparent indifference remained throughout the winter and he was idle all the time. In the spring of 1912, he went to a farm school and taught throughout the summer and gave satisfactory service.

On his return home in October, his condition grew worse, manifesting itself in a condition of secretiveness, leaving home early in the morning and remaining all day without telling anyone where

<sup>2</sup> Bianchi, Text Book of Psychiatry, 1904.



he had been. He was followed and it was discovered that he was frequenting houses of prostitution. At home he was indifferent to his children but obeyed the requests of his wife in a purely mechanical fashion.

On April, 2, 1913, he went to a Milwaukee sanitarium where he remained six weeks. Here the patient gave an account of the beginning of his trouble saying that in October, 1911, he experienced a feeling that everything about him had swelled up and was tremendously enlarged. This feeling was with him constantly and gave him such a sense of unreality that he was unable to work, unable to concentrate his mind upon anything and became unfit to do his class-room work. He did nothing in the winter of 1912 or 1913, because he had no power of concentration, no initiative and had a feeling of absolute inertia. At the sanitarium he responded well to all memory tests and physically showed nothing except very active reflexes. A diagnosis of dementia præcox was made and he was discharged May 30, 1913. In July, 1913, he was operated on for appendicitis after which he improved mentally.

On July 28, he was admitted to the Baltimore clinic. There the first few weeks his behavior was characterized by a state bordering on helplessness, weakness. He was easily fatigued but his speech was relevant, concise and correct. His memory for remote events was excellent. He was discharged, apparently recovered, August 23, 1913.

In September he began to teach in a small school and was very ambitious and enthusiastic for three or four weeks. He then became excited, talked incessantly about his work, was going to establish a boys' camp in several places for the education of boys. He was going to redeem some swamps in Illinois, and establish aquatic gardens and pipe water from the Atlantic Ocean so as to develop and cultivate salt-water plants and animals. He thought Rockefeller would supply him with funds, and wanted his wife to spend \$150 for a Victrola he could not afford. His personal property belongings instead of retaining their value of a few thousand dollars turned into a fortune of at least \$50,000. Soon he could not sleep well, became restless and reached a state where he would work all night on a typewriter. Specimens of his work showed misspelled words, grammatical errors, misconstructions, references to Jesus Christ as a teacher and as an individual misunderstood by his people.

About the first of November he talked incessantly and so rapidly that he finally became exhausted and sat working his jaws and making inarticulate sounds. He was apparently conscious and was not paralysed. About 2.30 a. m. he went to sleep for an hour, breathing heavily but did not have any noticeable convulsive movements. The following day he was again much excited and as talkative as before and could not keep still. He was taken to a Pittsburgh hospital where he remained seven weeks and was then transferred to the Baltimore clinic on December 22, 1913. He was overactive, excited and admitted it, but could not control himself. His memory was remarkable for its detailed and accurate account. He engaged in a dozen different enterprises at once, such as occupation work, all kinds of plans and schemes for his work of teaching, remodeling hospitals, and planned for a special train to take his school on an extensive tour of the West, in which he would employ certain physicians and nurses of the hospital for advertising purposes. He planned a series of litigations against the Pittsburgh hospital, wrote numerous letters and sent telegrams. He became more and more irritable and soon became involved in conflicts with other patients and attendants and finally attempted to break out. His physical status was excellent, the Wassermann reaction in the blood was always negative and he refused a special puncture. He was discharged February 19, 1914, and was taken immediately to the Kankakee State Hospital. He was quiet on admission but soon became restless, noisy and talkative. He was irritable and tried to assault one of the attendants with a piece of iron from a bedside table. He complained of being nervous and of suffering from in-

somnia. Asked to have his stenographer and typewriter sent down here. His ideas were somewhat grandiose in nature. He threatened to sue the eastern hospitals for detaining him and said they had him declared insane and sent here so his testimony would be incompetent. He had had an attack of dementia præcox in 1911, during which time his memory was poor and he had suicidal mania. After 18 months he recovered and attempted to make up the time he had lost but in so doing he worked too hard and in November, 1913, he lost control of his mind and could not stick to anything. He says he was infected with syphilis in the Pittsburgh hospital as a result of wearing contaminated bath robes, but denies ever previously having had a venereal disease, although he admits exposure. He spoke of having had bad dreams, such as that his wife was untrue to him, that his children were being cut up and mangled before his eyes, dogs were biting him, etc.

He gave a good account of his past life with dates, gave a fair account of his trip here and told what was done for him on arrival. His retention was somewhat poor, he was unable to remember either names or figures, although he recalled colors. At present he thinks his mind is clearer than it has been for any time in the last ten years.

Physically he complained of a little headache. The pupils were equal, regular and reacted well. The knee-jerks were greatly exaggerated, there was a fine tremor of the outstretched fingers.

On February 24, the Wassermann on the blood and spinal fluid was strongly positive. Butyric acid and Nonne-Appelt tests, strongly positive. Gold Sol positive, white cells 9. Other counts made on March 3, showed 12 cells; on March 28, 15 cells; on June 19, 7 cells; and on July 10, 5 cells. After several intraspinal injections of salvarsanized serum the Wassermann reaction on the serum and the spinal fluid became faintly positive and the globulin tests were also weaker.

We have here a man 45 years of age, who was a hard worker, a student, who was ambitious and who had always given satisfaction as a teacher. He was temperate, and as far as his family or he knew had never developed syphilis. When 42 years of age, he began to tire easily, lost interest in his work, became depressed. This condition improved somewhat the following summer, but in the autumn he was restless and began to frequent houses of prostitution; at home, however, he seemed still as apathetic and indifferent as before. He tried to teach the next summer but could not succeed. At a sanitarium where he was sent he complained of being unable to concentrate his mind on anything and of having a feeling of absolute inertia. Later, in the Baltimore clinic, he showed a tendency to fatigue easily, but no physical signs or speech defects. In September, 1913, two years after the beginning of his trouble, he became active, talkative, restless and expressed ideas of a somewhat grandiose nature. His typewritten work showed misspelled words, grammatical errors and misconstructions. In November, he had an attack of exhaustion, after he had talked rapidly for some time. This was possibly a slight epileptiform attack, although no definite convulsive seizures were noted. He continued talkative, irritable and at times threatened violence. After commitment he showed some memory and retention defects, exaggerated knee-jerks.

On studying the case with a knowledge of the later developments, one can see several things which might cause one to suspect an organic brain disease. The beginning of a mental disorder in a man of 46 who had never previously had an



attack is comparatively rare in the functional disorders, especially when the early history shows a past life unusually free from what we are accustomed to look upon as *predementia præcox* or manic-depressive states. In his hypomanic state the errors in typewriting in one who had been a teacher all his life must be regarded closely. The attack in November, 1913, in which he could not talk for a day was very suspicious. The lumbar puncture after commitment was made on account of the findings of a positive Wassermann reaction in the blood and on the suspicion aroused by the grandiose ideas and history of sexual excesses.

The second case shows a similar long period before paretic symptoms became marked enough to justify a clinical diagnosis.

#### CASE II.—J. E. A.:

*Family History.*—Paternal grandmother died in the Elgin State Hospital. Maternal grandmother died of cancer of the stomach. Paternal grandmother, chronic alcoholic.

*Personal History.*—The patient was born in 1876 in Indiana. Up to 12 years of age he was rather a weakling but not definitely sick. After that age he became strong and robust. Graduated from grammar school at 14 and was fully up to the average in his studies. After leaving school, he worked as a steam fitter, then as a railway fireman, saving his money until he was able to purchase a small store in Chicago which he has afterwards conducted.

He was earnest, hard working, ambitious in a small way and worked steadily towards making himself a competency. His habits were excellent and he hardly ever took any alcoholic drinks. He was rather retiring with regard to his personal matters but was always easy and natural in his behavior, mixing well with others of his own age and with both sexes.

Five or six years before admission he became entangled with a girl who clerked in the store for him and about a year later he sent her to someone to have an abortion produced. After this incident he continued to live with the girl for a short time but finally broke with her and dismissed her. Three years later he was married and on the day of his wedding he received a blackmailing letter from this other girl, which worried him very much at the time but to which he made no response.

About the time he became entangled with the girl he developed syphilis, and a year or so later he had an attack of jaundice which his physician found disappeared under treatment with potassium iodide which he had taken in the form of a patent medicine. He was then treated for three or four months when he discontinued it. Since that time his family have noticed that he has become more peevish, cross and excitable, easily irritated over small matters, which was quite foreign to his normal manner. At that time he weighed over 170 pounds, and without any definite illness he has seemed to be going down hill ever since, losing weight gradually and appeared more haggard. This was so marked that a year before admission he was sent by his brother to a physician who prescribed mercury for him. This upset his stomach and he discontinued it after a few doses. After that he continued to fail physically and would become so irritable that he was not fit to be in the store. He then began to read dime novels and neglected his work and became very angry if interrupted.

*Present Illness.*—On July 5, 1910, he went to help his brother move from one office to another and worked steadily with him for one week and part of the second week, then one morning he suddenly complained that he could not remember from one minute to another where to put the things they were moving, and it was found that in giving him instructions concerning where to put the different articles that he had forgotten the first part before the end of the instructions were reached, even when these were quite

simple. He became worried about this loss of memory, crying, and seemed much depressed and dull. He was sent home and became more anxious and depressed, so he was sent to a small private hospital. There he became anxious, very dull and heavy and had several outbreaks of apprehensive excitement in which he would scream as if in fear and would run away, speaking of someone pursuing him with the purpose of punishing him for his sins. As soon as the physician or his friends appeared he became quieter and begged them not to leave him, saying he was afraid and could hear people threatening him. He seemed, however, to be perfectly clear as to what had happened during the whole of his excited period. After an attendant was procured to stay with him these attacks of excitement disappeared to some extent, in the course of about ten days, but he was still somewhat apprehensive and evidently heard voices now and again.

In the intervals between these excited periods he was dull and heavy, complained that he could not think, that his mind was a blank, made occasional apprehensive allusions to the girl and talked in a vague fashion about her having had a baby and also questioned whether he and his wife had been regularly married. Gradually this picture of depression with difficulty of thought and marked slowness of action came to dominate the whole picture and continued up to the time of admission with occasionally a few hours in which he would be much brighter and said that he was feeling better.

His sleep was poor and disturbed by dreams, in one of which he heard a baby crying and also the voice of the girl, and when questioned placed the scene of the dream as somewhere in the country, on a farm, which he imagined was the home of the girl and he said she used to live in the country.

He was admitted to the Kankakee State Hospital on September 13, 1910. He accepted without protest or comment all that was done for him, showing little if any interest in the arrangements. When brought into the room for an interview he walked slowly, took his seat quietly, looked straight to the front. His eyebrows were contracted, lips closed, the eyes in constant motion but directed toward the floor.

When questioned he would move slightly, swallow several times, his lips would open and close again but only after several repetitions of the question would he utter a word. He was quite observant however, knew the name of the physician and told the time of day correctly. In response to questions he said he had pain in the head, that he was sad and that he heard voices which troubled him a great deal.

He was well oriented, could remember names, figures and colors given him but could not remember how long he had been in the hospital. He realized his mind was not clear and when asked if he thought he was insane, replied: "I guess I must be."

He required tube-feeding for some time after admission but later improved and his weight which was 90 pounds on admission increased to 176 pounds on April 19, 1911, at which time he had improved mentally a great deal, played cards and baseball, was interested in the affairs about him but was irritable and stubborn at times.

He was readmitted October 14, 1911, in a hypomanic state, was irritable and threatening. The pupils reacted sluggishly to light, the knee-jerks were equal and exaggerated. There was little or no defect in pronouncing test words. The spinal fluid showed a positive butyric acid and Nonne-Appelt reaction, the Wassermann reaction on the spinal fluid was strongly positive, on the blood positive.

He continued in a hypomanic, grandiose state for several months, then became depressed again and failed physically and died at home. At no time were memory defects marked and physical signs were never characteristic.

We have here a man of 34 years, who, when a child, was a weakling but who later developed well physically. He devel-



oped syphilis at the age of 29, and a year later had an attack of jaundice, which was relieved by potassium iodide. After that time he was more peevish, irritable and excitable than before. Physically he lost weight although he had no especial bodily complaints. While working with his brother one day he complained of not being able to remember, became depressed, anxious and somewhat dull. Then occurred an hallucinatory episode characterized by apprehensiveness and auditory hallucinations. The agitated periods subsided and were replaced by a marked depression with slowness of thought and action. On admission he was slow, rather resistive, answered questions only after several repetitions, required tube-feeding, but was observant and was well oriented with good retention. There were no marked physical findings except exaggerated knee-jerks. He improved and later developed a hypomanic state, was irritable, talkative and mildly grandiose. At this time the pupils reacted sluggishly and the spinal fluid showed a positive Wassermann and globulin reaction and the blood a weaker Wassermann reaction.

Here, as in the first case, there was some depressive ideas but the complaint of memory defects, the hallucinatory episode, the alertness in spite of the depression, would cause one to consider some condition other than a pure manic-depressive state and an allied dementia præcox condition. His reaction to mercury, the gastric complaints and later his physical failure, caused some to think of a condition caused by a mercury intoxication, especially since his hallucinatory episode so closely resembled a delirious state. After the disease had progressed so that physical findings were present, the diagnosis was comparatively simple.

Both of these cases showed predominating mental pictures, and the physical signs which would lead one to suspect an organic condition were few. Active or exaggerated knee-jerks were present in both cases, but this is not an uncommon finding in many of the functional disorders. In the first case, even after the disorder has existed for several years, the physical signs are not characteristic although they are suspicious. The history of syphilis in the second case would cause one to consider it as a possible causative factor, especially since the attack of jaundice occurring a year after the luetic infection was apparently benefited by potassium iodide. The psychosis was not typical and the apparent depression led to the grouping with the functional disorders, although it could not be placed definitely.

In the group of cases reported by Dana, the physical signs were more or less well marked and the diagnosis rested on the physical findings rather than on the mental picture. It is possible that our second case may be grouped with his diffuse

meningeal luetic infections, but in this case treatment with mercury did no good but rather led, apparently, to a physical decline.

That mental symptoms may occur early in paresis, there is no doubt. Syphilis may cause a transitory mental disturbance which may often precede for years the development of paresis; or, the latter condition may never proceed along its usual course. Remissions are common and may be of very long duration.

Whether these transitory mental attacks really are the early symptoms of paresis is not yet settled. In one case, in the hospital now, there were hallucinations, a feeling of well being and ideas of reference and persecution developing three years after a luetic infection. The Wassermann reaction on the blood was strongly positive, on the spinal fluid negative. The cell count and globulin reactions were negative. The patient has improved, has considerable insight and is in good physical condition. His mental disturbance lasted about a year, but at present he can be considered as recovered or in a state of remission. Whether he will develop paresis in the future or whether there are any changes in the nerve cells and fibers at the present time, we cannot tell. A study of similar cases and the collection of data along this line would be of great value.

The two cases reported show that paresis may occur without the ordinary physical signs which are emphasized in the text books. We do not, unfortunately, have any definite single mental picture which is pathognomonic, and consequently must rely to a great extent, in our doubtful cases at least, upon the laboratory findings. The lumbar puncture is now recognized as a means of clearing up some doubtful diagnoses and there is no reason why it should not be employed in every case where there is a question. In atypical cases, especially those with a history of a luetic infection, it should be obligatory. There is no questioning the fact that in the early recognition of paresis is our only hope of curing it, if there is any cure to be made.

In concluding we would urge the importance of obtaining a complete anamnesis of all cases, of weighing carefully the findings, mental and physical, in all atypical cases, of taking into consideration all possible clues in studying such cases and of using every available means, clinical and laboratory, in determining upon what basis the disorder rests. Just as syphilis may imitate any physical disorder so must we recognize the fact that general paralysis may at times resemble any mental disorder, and that it may exist for some time before physical signs are developed.

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## PATHOLOGY.

### DIPHThEROID INFECTIONS.

By C. H. BUNTING, M. D.,  
*Professor of Pathology, University of Wisconsin.*

My co-worker, Dr. Yates, and I have been rather freely criticized formally and informally for the part we have attributed to the diphtheroid organism in the production of Hodgkin's disease. Criticism has come because of the wide distribution of diphtheroids upon the mucous membranes of the body. Recognition of this fact caused us to delay publication of our results in Hodgkin's disease for over a year. It may not be out of place here "in the family" to give informally a reason for the "faith that is in us."

In the first place, it may be said that the diphtheroid organism has been cultivated by us from the glands in every case of un-rayed Hodgkin's disease in which attempt has been made. We have obtained it from the cervical, axillary and inguinal glands and from the spleen. We have obtained successive cultures from the same patient twice; in one case, after an interval of two years, and in the other, after an interval of 18 months. Dr. Rosenow (personal communication) tells me that in his series of about 40 cases the organism has been constantly present, and in four cases, when there was an acute exacerbation, he has obtained it from the blood. Further, in two cases of primary Hodgkin's disease of the intestine in children we have found by Gram's stain that diphtheroids were the only organisms within the wall of the intestine, and, moreover, were so situated as to explain the lesion. In one of these cases where the cæcum had been removed surgically, the organism was very widely distributed in the mucosa and submucosa, but no other type of bacterium was found.

From an experimental standpoint we have shown that in monkeys, rabbits and white rats, the inoculated organisms show an affinity for lymphoid tissue, producing changes in it in perfect agreement with those seen in early Hodgkin's disease. Further, in monkeys hæmatological changes have been produced similar to those found in human cases suffering with the disease. Such changes were produced also in a normal human being (Dr. Yates) upon subcutaneous injection of killed cultures. This inoculation showed further the marked stimulative effect upon fibroblasts seen in Hodgkin's disease.

Further, we have produced death in the monkey by inoculation of the organism. Death, however, has supervened too early to produce the chronic form of the disease. In this

latter point only have we failed thus far in the experimental proof.

As mentioned at the outset, the prevalence and wide distribution of diphtheroids seems to many an argument against their playing any part in Hodgkin's disease. We have obtained diphtheroids in the lymph glands of cases of lymphosarcoma (2), chloroma (1), arthritis deformans (1), associated with tuberculosis (1), recurrent erythema with glandular enlargement (1), in the spleen of Banti's disease (3). The relationship of these various stems is now being worked out. It may be said, however, that we have never obtained the organism from glands without some hæmatological or histological evidence of its activity, if we may assume that the changes in Hodgkin's disease are an expression of its activity. This was true even in the gland picture of the case of arthritis deformans. Others have obtained diphtheroid organisms in diverse conditions, Rosenow in lymphosarcoma, arthritis deformans, hyperplastic tuberculosis; Steele in leukæmia; Wolbach in leprosy, etc.

When we consider the varieties of streptococci and pneumococci, for example, it requires no great stretch of imagination to accept the possibility that there are diphtheroids and diphtheroids. Further, clinical and pathological evidence points to a close relationship between a group of diseases in which diphtheroids are most prevalent, *i. e.*, Hodgkins' lymphosarcoma, leukæmia, Banti's disease and the recurrent erythema group. We have seen the acute leukæmic blood picture occur in the course of cases of Hodgkin's disease and lymphosarcoma. We have had erythema with marked subcutaneous infiltration occur in Hodgkin's disease. We have found the diphtheroid organism in the ethmoid sinus and urine of a patient dying of acute nephritis following erythematous lesions of the legs and showing the early changes of Hodgkin's disease in the lymphoid tissue of the spleen. Our conception at present is that there are organisms of the diphtheria group of varied virulence, but all with a specific affinity for lymphoid tissue, including bonemarrow and its products, and that clinically and pathologically we have a varied reaction to the different stems. This conception, while attractive, requires proof.

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# THE MICROBIC CAUSE AND MANNER OF INFECTION OF POLIOMYELITIS.

By SIMON FLEXNER, M. D.

(From the Laboratories of the Rockefeller Institute for Medical Research, New York.)

## I.

About one year ago I had the privilege of presenting before an audience in this hall, for Dr. Noguchi and myself, the subject of the cultivation of the microörganism causing experimental poliomyelitis. To-day I wish to bring forward additional and, as I believe, important evidence bearing on the relation of that microörganism to the disease, infantile paralysis.<sup>1</sup>

Let me recall that the microbe in question was cultivated in a medium consisting of a fragment of kidney tissue and ascitic fluid under anærobic conditions in a manner similar to that employed by Noguchi for the cultivation of the parasitic spirochætæ. The microörganism cultivated from poliomyelitic tissues differs completely from the spiral organism mentioned, and appears as globular or oval bodies of extremely minute size, in conformity with the fact that the microbic cause of poliomyelitis is filterable and has hitherto been regarded as ultramicroscopic.

At the time that I reported the results of our experiments to the Johns Hopkins Medical Society—in this room—we could state that the microörganism had been cultivated from portions of the central nervous organs removed at autopsy from human subjects who had succumbed to epidemic poliomyelitis and from monkeys in which the experimental form of the disease had been induced by the inoculation of human tissues. The inoculations of the microörganisms which had resulted successfully were made with the third, fifth and twentieth generations of the cultures. The monkeys so infected developed the symptoms and the typical effects or lesions of the nervous organs characteristic of poliomyelitis; and, from the affected nervous tissues, the identical microörganism was recovered in cultures. Moreover, a filtrate prepared by passing through a Berkefeld filter an emulsion of the same nervous tissues was capable of conveying infection to other monkeys, just as the filtrate or virus from the original nervous materials derived from human subjects is capable of doing.

It was, however, found that of the different cultures of the microörganism obtained only a few were capable of causing experimental poliomyelitis upon inoculation; the greater number of cultures proving inactive or non-pathogenic. It was, moreover, quickly ascertained that the possession of pathogenic properties did not depend upon the generation inoculated; or, in other words, that an inactive culture proved non-pathogenic in the second as well as in later generations. This observation itself seemed to exclude some admixed indefinite "virus" as being the cause of the experimental infection when active cultures were inoculated and to connect the pathogenic

effect with particular strains of the cultivated microörganism under consideration.

There is nothing exceptional in this observation. All the data possessed indicate that the virus or microbe of poliomyelitis is highly parasitic; that is, resides and multiplies only within animals subject to its pathogenic action and not elsewhere upon living or dead things indifferent to its effects. When, therefore, such highly parasitized microörganisms are cultivated artificially they not infrequently quickly lose, wholly or in part, their pathogenic action.

Another possibility exists which may account for the lack of disease-producing power in certain strains of the cultures. The monkey is not, of course, a natural subject for poliomyelitis and is, on the whole, resistant to infection. On that account not all specimens of nervous tissues derived from human subjects of infantile paralysis can be implanted on the monkey; a percentage of strains of virus only of human origin are pathogenic for that animal. If, therefore, the cultivated virus or microörganism of poliomyelitis merely displays the original power of infection possessed by the human specimens a part only would be effective when inoculated into monkeys.

The new experiments bear also upon the survival of the microörganism in artificial cultures. Several tubes containing a pathogenic strain in the second generation were put aside for a year, at the expiration of which time the microörganism was still living. They were now subcultured and from the fourth generation in the solid medium of kidney tissue-ascitic fluid-agar fluid cultures were prepared as follows:

Into Erlenmeyer and Florence flasks of 75 to 100 cc. capacity, containing a fragment of sterile rabbit kidney, a layer 1 cm. thick of nutrient agar and ascitic fluid, previously inoculated with the culture and kept fluid at the temperature of 40°, was poured and allowed to congeal. Next, about 50 cc. of an equal mixture of bouillon and ascitic fluid were added and this overlaid with a layer 1 cm. deep of sterile paraffin oil. So prepared the flasks are incubated at 37° C. The microörganism multiplies first in the solid medium, from the large surface of which it penetrates into the fluid medium where multiplication also takes place. In from three to five days an abundant growth is obtained suitable for injection into monkeys.

The especial suitability of cultures so prepared for injection arises from two circumstances: the abundance of the growth and the great dilution of the materials employed for inoculating the culture. Indeed, the inoculated material is confined in the solid medium and gains access to the fluid, except through multiplication, very little, if at all. The quantity of culture employed in inoculating subcultures is about 0.2 cc., which is about the minimal effective dose of the original filtrate of an emulsion of nervous tissue derived from the para-

<sup>1</sup> Section I of this paper is based on an article by Flexner, Noguchi and Amoss appearing in the *Journal of Experimental Medicine*, January, 1915.



lyzed monkey. There can, therefore, hardly be a question of the activity of some merely admixed virus which is introduced into the monkeys, together with the cultivated microorganism.

The subcultures proved not effective in a single inoculation but became effective after several inoculations. The fluid containing the microorganism was injected into the peritoneal cavity or spinal membranes, once every six to nine days, the monkeys developing paralysis and succumbing after the fourth or fifth injection. The symptoms which arose resembled those of poliomyelitis, and the lesions present in the nervous system were characteristic of that condition.

At first sight this result may seem anomalous, but it is not so. The effects of successive injections of an active virus, as represented by filtrates of nervous tissues, may be such as to lead to no detectable change in the susceptibility of the animal, or to increase the resistance by establishing immunity, or to produce infection with paralysis and other lesions. Lewis and I noted that when an ineffective virus was injected into monkeys their susceptibility to a subsequent inoculation with an effective virus was not altered; and we also observed that in course of active immunization of monkeys by subcutaneous inoculations of the virus paralysis sometimes suddenly appeared in animals which had borne several inoculations previously without apparent inconvenience. The results, therefore, in this respect, of the several injections of the cultivated microorganism are fairly comparable to those of several injections of the ordinary virus, but there is still another respect in which they resemble each other. I have just stated that wholly ineffective injections of the ordinary virus leave the monkeys unaffected: they are rendered neither more nor less susceptible to subsequent inoculation with the active virus. Now, we have also observed that when ineffective doses of the cultivated microorganism are injected into monkeys the animal is not protected from an inoculation of the active virus. There remains, therefore, to make the analogy complete, to determine that under some circumstances the cultivated virus confers immunity as the ordinary virus sometimes does without causing any detectable paralysis whatever. Experiments along this line are in progress.

The deduction, therefore, is to the effect that the cultivated microorganism, separated from the nervous tissues for more than a year, and after many generations and indefinite dilution of the original materials subjected to cultivation, is capable, on successive inoculation into monkeys, of setting up the lesions accompanied by the symptoms of experimental poliomyelitis—a disease inducible in monkeys which accurately resembles epidemic poliomyelitis or infantile paralysis occurring in the human subject. The corollary to this deduction is to the effect that the microorganism in question is the microbic cause of poliomyelitis.

## II.

I have been requested to state why I regard the infective agent of poliomyelitis as being borne and disseminated by persons and not by insects. In the brief time which remains to me, I cannot enter into the details of this subject. I wish,

however, to remind you that the tracing of connections between cases of infantile paralysis showing frank symptoms of the disease has been a puzzling and sometimes an impossible task. This circumstance, taken together with the fact that rural, sparsely populated communities are often visited by the disease, which prevails especially in the late summer and autumn months, has led to the notion that it probably belongs to the class of infections conveyed by biting insects, which seemed the readiest way of explaining the phenomena observed. This view received for a time the support of experiments conducted by Rosenau and Brues and confirmed by Anderson and Frost. These investigators noted that under some circumstances the stable fly, having been permitted to feed upon monkeys inoculated with the virus of poliomyelitis, was capable of communicating the infection to healthy monkeys on which it was subsequently allowed to feed.

There is no question that in a few instances experimental poliomyelitis has been conferred by means of the bite of the stable fly. The experiments prove that under some circumstances the blood contains the virus, which can be removed from one animal and injected into another by means of an insect. Experiments made somewhat earlier by Howard and Clark had shown that the bedbug also can exceptionally remove virus containing blood from inoculated monkeys; but it proved impossible to induce paralysis by permitting the bedbug thus infected to feed upon normal monkeys. When, however, a watery filtrate was prepared from this insect and inoculated into monkeys paralysis resulted.

On the other hand, later experiments conducted by Rosenau and by Anderson and Frost, as well as by other investigators in this country and abroad with the stable fly, have failed completely to confirm the earlier successful tests.

Considerable light is thrown upon this question by experiments conducted with the blood which is removed by syringe from cases of acute poliomyelitis and injected into the veins of monkeys. Although many such experiments have been made, no one has ever detected the virus in the blood of human subjects of the disease. On the other hand, we succeeded in two instances in detecting the virus in the blood of monkeys, but only during a brief period in the course of the infection, a result confirmed by the finding of the minute microorganism in the blood by microscopical examination in one instance by Amoss. The conclusion therefore appears to be that under certain conditions the stable fly may perform the part of the syringe in withdrawing virus containing blood from the monkey and reinoculating it into other but healthy monkeys which in time may develop the symptoms and lesions of poliomyelitis. More than this, the few positive tests do not show; while the many negative ones indicate that the conditions mentioned are highly exceptional even for the monkey and, thus far, incapable of offering an explanation of the mode of infection of poliomyelitis in man.

On the other hand, the virus of the disease has been ascertained both to enter and to leave the infected subject by way of the naso-pharyngeal mucous membrane. It has been detected in that situation not only in frank cases of infantile



paralysis in man, but also in slight ones, abortive, so-called, and even in healthy persons who have been in intimate contact with active cases. Moreover, a few instances are known in which, after recovery, the virus was still detectable in the secretions of the naso-pharynx for several months. In other words, we have to do in infantile paralysis, as in so many other acute infections, with a series of factors which afford potentially ready means for the dissemination far and near of the microbic agent of infection. In this distribution the abortive cases, many of which are very little ill, doubtless constitute the greatest menace, although the passive and chronic carriers of the microbes, as the healthy or recovered but contaminated persons are called, who still continue to discharge infectious secretions from the throat and nose, play each an important and sinister part in this process. In this manner there can be explained, on the whole satisfactorily, the bizarre and puzzling appearance of cases of poliomyelitis, separated often by blocks or miles, between which no obvious intermediaries can be detected to connect one with the other. But connected they have been in notable instances by the tracing of the go-

between which have been ascertained to be of the kind just described, namely, abortive examples of the disease and carriers of the infectious agent.

The peculiarity of distribution just outlined is further illuminated by the fact that the human subject evidently possesses a high degree of resistance to infection with the microbic cause of poliomyelitis. This circumstance explains the sporadic appearance of cases, now here, now there, while many otherwise apparently susceptible persons entirely escape infection, or, responding, do so with such slight symptoms of illness as often to elude detection unless special attention be paid to their discovery.

These, then, are in brief the reasons why I believe the microbe of poliomyelitis to be borne by persons and not by insects. What the sanitary implications of the data set forth are is obvious, and since there exists no specific mode of treatment for infantile paralysis, and in view of the fatalities and the severe crippling which it causes, every effort should be put forth which promises limitation of the spread of the malady.

## CHONDRODYSTROPHIA FŒTALIS.

### NOTES ON THE PATHOLOGICAL CHANGES IN FOUR CASES.

By W. G. MACCALLUM, M. D.,

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The condition is one so well known and described in detail in so many recent papers that there is little excuse for any further description of cases which does not bring definite new information as to the ætiology or the mechanism of ossification. Nevertheless, the opportunity to study the organs of internal secretion and the peculiarities of the lines of ossification and the cartilage may justify what is intended as a preliminary to a further study, especially of the cartilage.

The first case was that of an old woman from whom no history of the occurrence of any similar deformity in her family could be elicited. She was moderately intelligent and could care for herself and perform ordinary housework, but was irascible and quarrelsome. No especial clinical history could be obtained, but the autopsy revealed the following:

**ANATOMICAL DIAGNOSIS.**—Achondroplasia—great obesity. Shortening of all long bones. Atrophy of epiphysis cerebri.

**History.**—Catherine D., aged 75 years. The body is that of a most extraordinarily deformed woman 45 inches (112.5 cm.) in length (Fig. 1). The head is enormous with nose flattened back so that the nostrils look almost straightforward. Forehead large. Cheeks fat and puffy. There are two teeth in the upper jaw and none in the lower. The body is enormously fat—must weigh 150 pounds or more. Arms are absurdly short reaching scarcely to the umbilicus. The legs are similarly short and the hands and feet short and thick.

#### *Measurements:*

Upper arm 17½ cm.

Forearm 15 cm.

Hand to tip of finger 15 cm.

Crest of ilium to external malleolus 57½ cm.

Head (occipital protuberance to glabella) 58 cm. cir.

Antero-posterior measurements 31 cm.

Transverse measurement from ear to ear 31.5 cm.

Length of face 31.1 cm.

Nostrils 4 cm. wide

Circum. of thigh 60 cm.

Sternum 15 cm. in length

On incision the subcutaneous fat is very abundant, 5 cm. over the abdomen. The peritoneal cavity is dry and the surfaces smooth. Omentum, mesentery, etc., enormously loaded with fat. Appendix is long and cord-like—its mesentery swollen with fat. The pelvic organs are quite free of adhesions.

The chest is very short. The costal cartilages are apparently ossified but very soft and easily crushed through. No distinct swelling of costochondral junction. Diaphragm at fourth rib on right, fifth space on left. Pleural cavities are free of fluid. No adhesions. Pericardial cavity contains no fluid. No adhesions.

**Heart.**—Not enlarged and very soft. Its surface is smooth and covered with fat. Relatively little blood escapes on incision. The endocardium is everywhere smooth. The mitral valve is slightly thickened and shortened—not obviously insufficient. The aortic valves are slightly thickened but competent. The other valves are delicate. The heart muscle is dark red and very soft.

**Lungs.**—Not very voluminous. The pleural cavities are relatively small. The bronchi are calcified in their large branches and in their main trunks. On section the lung substance is dark red, somewhat œdematous in places but otherwise air containing throughout.

**Thymus.**—A great mass of fat lies in the anterior mediastinum and the whole was kept for further study but no definite thymus tissue could be made out.

**Thyroid.**—The gland measures 4 x 3 x 1 cm. on the right, slightly less on the left. Its tissue is of normal color, soft, with



little colloid and not scarred. Two *parathyroids* were found toward the lower pole to the median side of the thyroid. They measured about 9 x 5 mm., were very thin and flat and brown. The other two have not yet been found.

*Carotid Glands.*—Were preserved and seem not enlarged nor especially altered.

*Lymph Glands.*—Were not enlarged in the neck and very few were found—one or two were deeply pigmented. Nothing abnormal was seen in the tongue or pharynx.

*Spleen.*—Was rather large and soft. Measures 11 x 6 x 4 cm. All the elements were plainly visible.

*Pancreas.*—Embedded in fat. Its tissue looked rather soft and oedematous. The pancreatic duct is easily traced to the papilla.



FIG. 1.—Sketch of the body of the first case of chondrodystrophy. A woman aged 75.

*Liver.*—Weighed 2¾ lbs. (1350 gm.). The left lobe is very small. The right on section shows a soft rather shrunken liver substance with much fat content. The acini are indistinct in outline. The gall-bladder contains a large calculus which fills the whole bladder. The cystic and common ducts are normal.

*Stomach and Duodenum.*—Normal. Small intestine and colon not opened. Rectum normal.

*Adrenals.*—Are irregular in outline. Not notably altered in size. The cortex is readily torn apart so as to leave a cavity in place of the medulla. In the irregular cortex are many irregular nodules. Left measures 4.5 x 2.5 x 0.5 cm. Chromaffin nodules are preserved along the gangliated cord.

*Aorta.*—Is distinctly inelastic and rather uniformly set with small patches of sclerosis throughout its whole length. It is 4 cm. in circumference in the mid-lumbar region. Other arteries, in-

cluding carotids even into the cavernous sinuses, very sclerotic and dilated.

*Kidneys.*—The left measures 11 x 5 x 5.5 cm. Buried in fat. Capsule strips off easily and smoothly. Surface is rather swollen looking. Lobulations are normal. On section the blood-vessels are rather thick. Cortex is 7 mm. in thickness, striations straight.

*Bladder.*—Normal.

*Uterus, Tubes and Ovaries.*—The ovaries are of moderate size and very little scarred for their age. The right measures about 1.5 x 1 x 1 cm. The left is rather larger, 2 x 1.5 x 1 cm. On section there are some old remains of corpora lutea. The ovaries are not unduly atrophied. The tubes are normal. Uterus is of normal size and appearance. Measures about 7 cm. in length. There is a rather curious soft elongated mass, apparently of muscular tissue, without lumen in the situation of the left round ligament. The mucosa of the uterus is gray and moist and contains some small cysts.

*Pelvis.*—Is greatly contracted. The internal conjugate diameter (promontory to symph. pubes) measures only 6 cm. The transverse inner diameter is 10 cm. The birth canal will admit only three fingers in the antero-posterior direction.

The femur (preserved) is phenomenally short (22 cm.). The extremities are slightly enlarged.

Nothing abnormal could be seen in the vertebral column although the antero-posterior curves were rather marked.

*Brain.*—The dura is very adherent to the calvarium which is thickened somewhat. The base of the skull was not carefully examined but seemed very slightly if at all divergent from the normal. The foramen magnum was about the normal size and the spinal cord was not encroached upon. The sella turcica was very slightly enlarged, chiefly to hold the dilated and sclerotic loops of the carotid arteries. The *hypophysis* is in gross about normal in size, form and consistency.

The surface of the brain is marked by great atrophy of the convolutions and widening of the sulci which were filled with fluid. The oedematous pia was pigmented in places with yellow granular pigment.

On section the cerebral ventricles were found markedly dilated with clear fluid. The third ventricle is widened and a commissure extends across it as a free cord. The *epiphysis* or pineal gland is reduced to a minute almost transparent fragment of tissue upon its recognizable stalk. It does not seem to be one-twentieth as large as it should be. Spinal cord not removed.

Microscopically, the organs showed little if any abnormality. Hypophysis, parathyroids, adrenals, pancreas, carotid glands and ovaries seemed perfectly normal. The pineal gland as stated was very small, not more than 2 mm. in diameter, but so far as it is preserved its structure is normal. It seems probable that the decrease in size may represent a senile change. The thyroid shows microscopically only such changes as are very commonly seen in the thyroid of old people, namely, a slight scarring or increase in the density of the fibrous framework. The epithelial cells are desquamated in some alveoli and colloid is not abundant, but on the whole it seems functionally competent. The femur and a rib were studied microscopically but except for the rarefaction of the cancellous bone, also incident to age, no abnormality could be observed. Naturally, the epiphyseal line was no longer to be made out and the articular cartilage appeared normal.

Nothing could be learned then from the conditions of the organs in chondrodystrophy at such an advanced age to throw any light on the nature of the disease, except that all of the organs of internal secretion seem normal and that the remaining organs are also normal. Evidently nothing is left after the cessation of growth in the bones to explain the perversion of that growth.

The other three cases were in infants, two of which were found in the museum of the College of Physicians and Sur-



geons, while the third was a premature child at about the seventh month, born of apparently healthy parents. The autopsy on this case was performed by Dr. A. M. Pappenheimer who gave me the material.

The two infants found in the museum had been preserved in alcohol for many years and no history was available. The internal organs were softened and useless for microscopical or even gross study, so that nothing can be said of their organs of internal secretion. The base of the skull and the long bones could be investigated, however. In the third case, born of healthy parents, the thyroid was quite normal, except for a slight desquamation of the epithelial cells. The parathyroids were normal. The thymus was of normal size, its medullary portions rather indistinctly marked out against the cortex. The adrenals, pancreas, spleen, liver, etc., showed no abnormalities. Unfortunately the hypophysis and pineal gland were lost at the autopsy and could not be studied.

In all three there was extreme shortening of the arms and legs. The head was relatively large but the deformity or retraction of the nose so commonly met with was not particularly striking. Vertical sagittal slices were cut through the base of the skull in each infant and cleared up by the method of Spalteholz. These showed that in every case the two portions of the sphenoid bone and the basilar portion of the occipital bone were widely separated by cartilage, so that in these cases, at least, the premature synostosis described by Virchow and held accountable for the retraction of the nose has not occurred. Kaufmann points out that it occurs in only a part of the cases. Bones were excised from each case for study. The femur was in every instance extremely short, the incurved shaft appearing extremely small in contrast to the large masses of epiphyseal cartilage, which overhang it almost like a cap on all sides (Fig. 2). The cartilaginous trochanter in each instance seemed disproportionally large, so that the head of the femur appeared as a small projection beneath it.

On cutting through the femur longitudinally the shaft was found to be very dense and hard and the periosteum thick. The cartilage, in which of course no centers of ossification had as yet appeared, was not particularly softened, although microscopical examination revealed a change in the structure somewhat resembling that described by Kaufmann and by Marchand and Kirchberg as chondromalacia.

This was true of the first and third cases which were so much alike that they may be described together, while the second case presented a different appearance.

In the first and third of the infants longitudinal microscopical sections through the femur and tibia showed the following: The periosteum of the shaft forms a thick layer under which a dense bony wall is deposited. Within this cortex the cancellous bone which makes up the shaft is extremely compact and dense even though many of the lamellæ contain some central remnants of cartilage. The periosteum is prolonged past the end of the ossified material and turns inward as a spur into the substance of the cartilage, although it does not extend far. This evidently represents the periosteal lamina described by Urtel, Kaufmann and many others as forming a barrier

against the endochondral ossification. Much dispute has taken place as to whether this were merely an inclusion of the periosteum or an active ingrowth. In these cases it extends so short a distance that in itself it could hardly interfere much with ossification—instead it appears to be merely the end of the periosteal sheath of the shaft over which the exuberant cartilage has poured down the outside like overflowing paraffin which solidifies.

Study of the cartilage shows that in all the distal parts, and especially perhaps in that which extends backward outside the periosteum, there is a peculiar disappearance of the normal homogeneous matrix, so that the cartilage cells are single or in little groups which hang together in a network. In the meshes there are numerous fibrils and many branching cells surrounded by fibrillæ. Indeed, in places, and especially about the numerous blood-vessels, the cartilage is transformed into a felt-like connective tissue, throughout which groups of cartilage cells are scattered. This is very different from the distal parts of the normal epiphyseal cartilage in which the elongated spindle-shaped cartilage cells lie in every direction, but closely embedded in the homogeneous matrix. It will be seen from the drawing that this overflowing of the cartilage removes much of it from a position in which its cells might eventually be presented for invasion by the marrow spaces and, indeed, leaves the end of the shaft of the bone covered by a relatively thin layer of cartilage. Probably much of what seems an excessive production of cartilage is, through this softness and shifting from the range of the ossification process, rendered useless for the further growth of the bone.

In the remainder, as the time of ossification is approached, a preparatory zone becomes recognizable, in which the cartilage cells are flattened and arranged in columns which run vertically to the line. Although in the normal this perfectly regular phalanx is maintained in spite of the swelling of the cartilage cells, it is rather different in these cases. The columns lose much of their regularity and the invading marrow spaces with their blood-vessels become correspondingly irregular, so that the line of ossification, while in general fairly even, is vague and indefinite. The ossification process obviously continues but varies in intensity at different points. In some sections, and especially in those through the costochondral junction, the line of ossification is exceedingly irregular (Figs. 3 and 4).

Not only is the order of the cells destroyed but the process itself seems somewhat modified. Quite extensive calcification of the cartilage matrix is found between the unaltered cartilage cells, and ragged branching masses of this calcified material, often including cartilage cells, are found to extend quite down among the lamellæ of the cancellous bone. These gradually become ossified by the application of osteoblasts, but imprison for a long time the cartilage cells which were included in their central parts.

Thus, if somewhat slow and irregular, ossification does still go on and produces dense cancellous bone. From the section, however, it is impossible to say how much cartilage is actually presented for ossification in this way and it seems that it is





FIG. 2.—Section of femur of infant, Case 2, showing abnormal arrangement of cartilage and periosteal spurs.



FIG. 3.—Costochondral junction, Case 2, showing irregularity of the line of ossification and extensive calcification of cartilage.



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FIG. 4.—A portion of the same more highly magnified, showing lack of column formation in the cartilage. Periosteal bone formation extends some distance past the line of ossification.

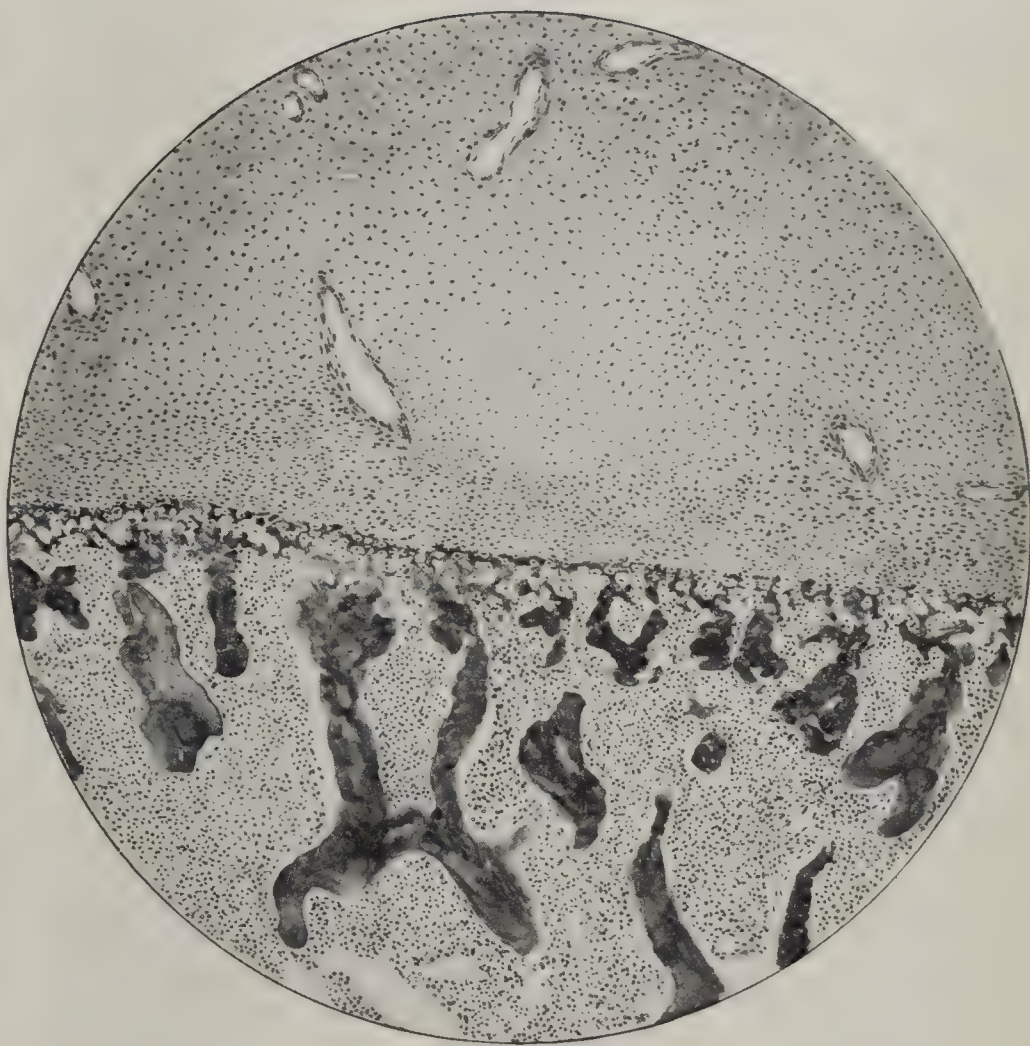


FIG. 5.—Line of ossification of femur in Case 3, showing a lack of column formation in the cartilage and consequent lack of ossification.







on that that the extreme retardation in the longitudinal growth of the bone depends.

The second infant was very badly preserved and the details can hardly be made out in sections of the bones. Nevertheless, it can be seen that the process is rather different from that in the other two. The cartilage at the ends of the excessively short bones is abundant but does not pour over the ends of the bone shaft in the way described for the others. Microscopically, it is not found to differ markedly from the normal, being composed of a complete and homogeneous matrix in which the cells are embedded (Fig. 5); but the preparatory zone presents no columns of cells. The cells are all flattened it is true, but they form no columns even quite down to the ossification line nor swell up as they do in the normal; consequently, the line of demarcation between cartilage and bone is perfectly even and is composed on the one side of flattened cartilage cells which present an unbroken front to the marrow cavity. At the very margin there are some which have become calcified with the matrix into a layer which is continuous at places with masses or laminae of what appears to be calcified cartilage from a previous epoch when ossification was proceeding more actively. Lower still these fuse with dense bony

laminae. Here the endochondral ossification seems to have been at a standstill at the time of the child's death and probably this accounts well for the extreme shortness of the bones. The shaft of the femur was less than 1 cm. long, although the child was at full term or thereabouts.

These alterations in the process of ossification, even at their severest, seem far less calculated to check the growth in length of the bone than such destructive changes along the line of ossification as are seen in congenital syphilis. Even in infantile scurvy, or in rickets, the disturbances of endochondral ossification seem more severe than those in chondrodystrophy, and yet they have relatively little effect in shortening the bones; while the chondrodystrophic, if he survives, is a dwarf. The explanation probably lies in the fact that although the line of ossification is somewhat irregular, ossification is not really in abeyance. It proceeds with all vigor on the part of all the other osteoblasts and in the case of the line of ossification; the fault lies undoubtedly with the cartilage which fails to present its cells in orderly fashion and rapidly enough to produce a bone of normal length or to keep pace with the periosteal growth. Why this is so is not yet clear but it is enough to justify Kaufmann's term *Chondrodystrophia foetalis*.

## GYNECOLOGY.

### THE ORIGIN, GROWTH AND FUTURE OF MEDICAL ILLUSTRATION AT THE JOHNS HOPKINS HOSPITAL AND MEDICAL SCHOOL.

By MAX BRÖDEL.

The Twenty-Fifth Anniversary Celebration of the opening of The Johns Hopkins Hospital seems an appropriate time to sum up the work done by the art department of the institution; to tell how it began, how it developed and what it hopes to do henceforth. Since I have been intimately identified with this department from the start, it is impossible to describe it without referring to the part I have played in its development.

When I arrived on January 18, 1894, there was no artist in the institution. Dr. Kelly had begun to write his "Operative Gynecology," for which I was to draw the pictures. Mr. Anthony Murray had made a series of photographs, illustrating the various steps of operations. These photographs formed the basis of the first set of drawings I made. Soon, however, I realized that emancipation from the camera is an absolute necessity for the medical illustrator, and, after a few months, I completely rejected photographic aid. As I was then the only illustrator in the institution, Dr. Kelly was asked from time to time by members of the other staffs to lend his artist. I undertook their work reluctantly, for while I knew little of gynecology I knew still less of the other branches of medicine. These illustrations were not very successful, and I often wished that I had not attempted them. Most of my previous training had been along different lines. Medical illustrating

was entirely new to me; it seemed enormously complex and obscure. To make this clear, I will describe simply what this previous training had been.

From 1885-1890 I went through the Gewerbe Schule and Kunst Akademie at Leipzig as a regular pupil, first studying the basic principles of all art work. I then copied originals, drew from the cast and finally from life. As was the practice in those days in Leipzig's Academy, some of the pupils spent part of their time acquiring one of the graphic arts. I selected lithography (*i. e.*, drawing on stone); others, wood engraving; and again others learned etching and copper engraving. To this training in the graphic arts I attribute in a measure the development of the technical side of medical illustration, as we have practiced it in this school. Modern photo-mechanical reproduction demands an original of a high degree of technical finish, for any slight defect becomes exaggerated in print. I well remember the many weary months spent in the lithographic department. The hand stippling in chromo-lithography was particularly trying. It seemed so useless to me to spend many days placing millions of little dots, the aggregate of which represented the yellow plate of a landscape, a color so faint that it hardly showed in the print. Then came a grey, a blue and so on through 12 to 20 colors, each on a separate stone and each stippled in by hand. My friend



Horn, who had the adjoining desk, also found the work very trying, but we went through it all, and I have since felt that it did us a great deal of good, for it gave us the patience which is so necessary in the face of a prolonged task, as, for example, a microscopic picture. Besides, we all acquired a steadiness of hand and a control of line, which has been one of our most useful assets in medical drawing.

Until 1893, I had no idea that I would ever become a medical illustrator. My selection of this specialty was wholly accidental. The summer vacations were usually spent in drawing or painting what we liked, viz., faces, figures or landscapes. One summer I spent modeling with a sculptor; another found me painting mural decorations in a public hall and a restaurant. Our greatest joy was tramping through woods and meadows in search of motives until we happened upon a pleasing group of trees, an old tumbled-down mill or a little waterfall. There was no sale for such pictures, but there was joy in making them. All the money I earned in those days was for portraits I drew or painted for relatives or friends and that barely paid for the materials. In the summer of 1888, when Prof. Carl Ludwig of the Physiological Institute in Leipzig needed a color microscopic picture of a section through the brain cortex enlarged about 150 times—Ludwig's artist not being available—the director of our school recommended me as a substitute. I was sent for, and Ludwig explained the section. The portrayal of all the cells in a strip six inches wide and a yard long was an enormous task. There was no camera lucida in those days, and no other mechanical aid. Ludwig was very exacting, each cell had to be a faithful copy. I worked many weeks to make that one drawing, my first medical picture, and I believe the hardest I ever attempted. The following summer I made about 15 drawings of the heart for Prof. Ludwig and Dr. Krehl, and several large topographical drawings for Prof. Wilh. Braune, of the Anatomical Institute.

I was, however, not properly equipped to do such work except in regard to technique, which gave me little trouble. Of medical matters, I knew almost nothing. Often since I have marveled at the patience with which the great Ludwig explained the heart to me. I did not know then that the only way to plan a picture is to leave paper and pencil alone until the mind has grasped the meaning of the object. I blundered when I relied on faithful copying alone. Copying a medical object is not medical illustrating. The camera copies as well, and often better, than the eye and hand. Naive copying is probably correct in other art work, where it may even have its virtue, but in medical drawing full comprehension must precede execution.

In those days Ludwig's laboratory was the Mecca for medical men of all classes and all countries, and it was there I met, for the first time, Dr. Welch and later Dr. Mall. For Dr. Mall I make drawings of the reticulum and for Dr. Halsted drawings of goiter. I heard of the plans that were being made by the Hopkins, and after hesitating for two years I decided to come to this country. My parents and friends also urged me to do so. My original intention was

to return in a few months, or in a year at most. I well remember my disappointment when I arrived. The work was totally different from anything I had ever done, and Baltimore, in those days, was an unattractive city to me. However, its people were kind. They made the place homelike, and the uncongenial work interesting. As stated before, my first work was on Dr. Kelly's "Operative Gynecology," with many illustrations on other subjects to interrupt the routine work. Drs. Cullen, Clark, Halsted, Mall, Barker, Russell, Ramsay and others wrote articles requiring pictures, which I usually did at odd hours after the day's work was done.

About a year after my arrival, Hermann Becker, my friend, came to assist me in the work. His training had been identical with mine, excepting that he had taken up wood-engraving. His tendency was in the direction of minute detail work, which rendered him particularly fitted for microscopic drawing. As the years went by he developed into a master in this specialty, his work for Cullen's "Cancer," and Kelly-Hurdon's "Appendix" being by far the best in medical literature.

In 1898, my old friend and colleague, August Horn, arrived. His training, also, had been the same as mine. In addition he had enjoyed the advantage of several years' study in Munich and Italy. He soon proved his worth, for his water-color drawings of breast tumors for Dr. Halsted and Dr. Bloodgood were among the best examples of such pictures in existence. Unfortunately, they have for years been exposed to too much sunlight, which has bleached some of the delicate tints. But still they are an eloquent testimony to the realistic conception, artistic pose, effective illumination and minute care which were the main characteristics of Horn's work.

For several years Becker, Horn and I worked thus together, each interested in his own field and following his own trend. We often severely criticized each other's drawings, a habit which, among friends, cannot help being of benefit. Each tried to profit by the experience of the other. The success of one proved an inspiration to the rest. Failures became problems, the solution of which concerned all three. But although one thus learned from the other, each retained his own characteristic style.

I must here mention a factor, which contributed largely to the success of our work. It was Dr. Kelly's habit to sketch for us in a few primitive but graphic lines the different steps of his operations. An artist finds it always harder to plan a drawing than to make it. The selection of the best view, to find out what to show and how to show it, that is what makes the artist hesitate and lose valuable time. Without question, Dr. Kelly's genius for sketching has in the beginning often paved the way for us. He laid the foundation of our development in this important part of our work, viz., a conception of the picture.

I realized that independence of judgment and originality of conception were only to be gained by original study. With Dr. Kelly's permission, I therefore set to work and systematically and repeatedly dissected, injected and studied the regions which concerned us in our work. I found that he who makes



a dissection or operation automatically obtains a series of vivid mental pictures, which serve admirably as guiding images during the subsequent task of drawing. I found also that preliminary dissection means greater speed in drawing, bolder and more artistic results; while lack of original study means hesitation, labored treatment of drawing, timid result. Nowhere to my knowledge had it been customary to grant to the artist time and opportunity to practice preliminary original study, and I feel that much of the credit for the success of our illustrations should be given to Dr. Kelly for his liberality in this respect. This practice was of benefit also, in so far as it resulted in greater uniformity between pictures and text, for the bulk of the anatomical and embryological chapters were written by the artist. He had made the research and the pictures; it was but logical to let him write the text.

A few words should be added in regard to some of the various techniques developed in the art department. When I left Germany all medical drawings were made in a laborious manner in lead pencil, crayon or India ink, on ordinary drawing paper, or else painted in water colors on Whatman paper, while elaborate pictures were painted in oil. It usually required several days of steady work to finish an average-sized drawing. The newness of the subject-matter compelled me for a few months to concentrate my attention upon it and adhere to the old techniques. But about the fall of 1894, I began to experiment with new media which promised better and more speedy results. A swifter technique always means a more artistic picture. Many drawings were now made in various new combinations of materials. The main stumbling block was the insertion of high lights to represent the glistening characters of fresh tissue, also vessels, nerves and delicate structures of all kinds, upon which, in medical drawings, so much depends. To "spare" them out, leaving the paper white, was too laborious. Rubber did not erase them clean enough, a knife made them too rough, while white paint looked harsh and also proved unreliable in reproduction. The difficulties suggested the use of a paper coated with chalk or china clay, and having a granular surface. Out of a large variety of such papers, I finally selected Ross' hand stippled drawing board No. 8, and a smooth scratch board, which combined all the virtues I was looking for. Of course, the first group of drawings made on such paper was still crude, but soon better results were obtained, until it became evident that for medical drawings of all kinds this medium is by far the most suitable. The technique is easily acquired, even by a novice, who never fails to be surprised with the splendid results. All drawing materials can be used on this paper, even water color. It lends itself very well to the representations of textures of all kinds. High lights are lifted out first with a hard rubber, then with a scraper. If too brilliant they are quickly subdued with a dry brush and crayon dust, and the process may be repeated if necessary. The chalk coat is thick enough to permit six or eight successive scrapings over the same spot before the chalk surface is worn through. If the drawing is bent, the chalk surface will crack. For this reason, every drawing should be mounted on stiff cardboard. This, however, is not the place to describe the method in detail.

A few words should now be said regarding my method of sketching and transferring the sketch, which also has resulted in great benefit to us. Hitherto a drawing was either faintly sketched in lead pencil and then strengthened and elaborated on the same paper, or the sketch was transferred to another sheet with carbon or blue paper, by going over every line with a blunt steel point. There are several such processes, all of which are time-consuming and inaccurate. It was in a measure accidental that I discovered the value of a fresh crayon sketch as a means of direct transfer without the necessity of hand tracing. An unrubbed crayon drawing permits of a perfect transfer upon a smooth paper surface by simple pressure with the thumb-nail upon the reverse side. So clear and strong is this negative transfer, that it can in the same manner be transferred upon the finishing paper, yielding again a positive. This is an exact replica of the original sketch, just as clear, only fainter. No time-consuming hand tracing is necessary, all being done in a few seconds with the pressure of the thumb-nail. This copy now forms the basis for the finished picture, be it black and white, colored or pen-and-ink. I have found such a faint plastic tracing particularly useful as a basis for pen-and-ink drawing. Its presence facilitates greatly the swift and correct placing of the pen strokes. After the completion of the pen drawing the faint tracing is easily removed with a rubber or art gum.

All planning of the drawing, all corrections and changes are made on the sketch. Very extensive changes are made with scissors, the rejected portions cut out, the accepted parts pasted on a clean sheet of sketch paper in the same or changed position as the case may be, and the sketch continued until it is satisfactory. To this method of sketching everything in crayon and double transferring the sketch, I attribute in a large measure the speed of our work. I have kept all my old sketches for 21 years, and often have I found them useful as a basis for new drawings, thus saving valuable time. A great number of the sketches have never been finished. It frequently happens that an interesting case may be followed in a few weeks by one still more so. This has caused me to adopt, in some instances, the policy of waiting for a time before finishing the drawing.

Our activity continued thus for many years. Thousands of pictures were made to illustrate the various books and many articles written by the faculty and staffs of The Johns Hopkins Hospital and Medical School. To save time I shall enumerate only the books, some of which contain several hundred pictures.

TITLE OF BOOK.	AUTHOR.	ILLUSTRATORS.
Operative Gynecology, 2 vols.	H. A. Kelly.	Becker and Brödel.
Hydrosalpinx.	Thomas Cullen.	Brödel.
Cancer of Uterus.	Thomas Cullen.	Becker and Brödel.
Welch Festschrift.	Pupils of Dr. Welch.	The several authors, Becker and Brödel.
Appendix.	Kelly-Hurdon.	Miss Huntington, Becker and Brödel.
Medical Gynecology.	Kelly.	Horn and Brödel.



TITLE OF BOOK.	AUTHOR.	ILLUSTRATORS.
Gynecology and Abdominal Surgery.	Kelly-Noble.	Becker, Horn and Brödel.
Adenomyoma of Uterus, 2 vols.	Thomas Cullen.	Horn, Becker and Brödel.
Operative Gynecology, 2 vols., second edition.	H. A. Kelly.	Horn, Becker and Brödel.
Myomata of Uterus.	Kelly-Cullen.	Horn, Becker and Brödel.
Kidney.	Kelly-Burnam.	Brödel.
Diseases of the Umbilicus. (To appear shortly.)	Thomas Cullen.	Horn and Brödel.

There are several other books, the illustrations of which were made by my pupils, or under my supervision, or to which I have contributed a limited number of pictures. They are as follows:

TITLE OF BOOK.	AUTHOR.	ILLUSTRATORS.
Malarial Fevers of Baltimore.	W. S. Thayer.	Brödel.
Obstetrics.	J. W. Williams.	Miss Montague and Lockwood.
Nervous System.	L. F. Barker.	Brödel.
Clinical Medicine.	C. P. Emerson.	Miss Huntington, Lockwood, Becker and Brödel.
Essentials of Medicine.	C. P. Emerson.	Emerson.
Diseases of the Heart and Aorta.	A. D. Hirschfelder.	Hirschfelder.
Studies in Gynecology.	J. A. Sampson.	Sampson.
Embryology.	W. E. Kellicott.	Didusch.
Diseases of the Ear, Nose and Throat.	H. O. Reik.	Morrison.
Development of the Vascular System.	H. M. Evans.	Evans.
Surgery of the Vascular System.	B. M. Bernheim.	Didusch.
All the Mayo Clinics.		Miss Byrnes, Miss Peters, and Fry.
Many of Dr. H. Cushing's Publications		Cushing.
Clinical Medicine.	L. F. Barker. (All new illustrations.)	Shepard.
Archives of Embryology—Carnegie Institution. (To appear shortly.)		Didusch.

This list, though incomplete, serves to bring out the fact that the work of the art department had extended far beyond the sphere originally set for it and developed into a school for medical illustrating.

I have always felt that the training of other artists is more important than the mere making of pictures; consequently, I always gave much time and thought to the instruction of any one, artist or amateur, who was interested in medical illustrating. I found talented pupils not alone among artists but also among the medical faculty and medical students. So I began about ten years ago, when still in the employ of Dr.

Kelly, to devote several hours each week to the teaching of research workers of the various staffs. Each of them was interested in some special kind of work requiring illustrating, and I helped to find suitable pictorial expression for their ideas. While some were very talented, others had to be taught the rudiments of the art. I enjoyed the work, and with few exceptions it was a success; many of the illustrations made by the first group of illustrator-scientists being printed in the literature.

This encouraging experience with the staff made me confident that still more good could be done by trying to reach the medical student in his first year. No one doubts the usefulness of sketching during the study of medicine. It makes the student a better observer, and gives him a better memory of facts, forms and relationships. Consequently, he does his studying more quickly and thoroughly. Such a student always gives greater promise of later developing into a research worker or teacher. As discussion of an obscure matter makes it clearer, so sketching and drawing make a complex structure more easily comprehended.

While I gave general instruction of a technical nature to the whole class, in order to help their sketching in histology, gross anatomy and, later, pathology, I gave special instruction to the few more talented students. But concerning this more later.

Thus the work went on. I did my routine work, illustrating for Dr. Kelly and his associates and devoted, with Dr. Kelly's permission, a small part of the time to teaching. Horn and Becker did no teaching. Each book as it was published marked a milestone in our career. In 1909, Horn became ill and after a lingering sickness he returned to Germany and died August 19, 1910, in Bad Nauheim. Then Becker's health unfortunately became somewhat impaired and after he had finished the drawings of the Kelly-Noble book, he was obliged to abandon his work, temporarily. My work for Dr. Kelly was completed December, 1910, and I also was called upon to consider the question of severing my connections with the institution. Naturally, I was loath to do so. There was much congenial work still to be done, many plans I had laid required time and sustained effort to mature, and I knew that if I left, much that had been started would probably be abandoned. Horn's untimely death and Becker's illness had left me the sole representative of the art department. Up to this time, no art department, as such, had any official recognition. There were no funds for the purpose, our salaries being paid by Dr. Kelly. Then Dr. T. S. Cullen conceived the plan of placing the department on a permanent basis, by obtaining an endowment fund, and succeeded in interesting a prominent citizen of Baltimore in the plan. This anonymous friend of the university has furnished the funds to continue the work for five years with the hope that in the meantime the chair may be permanently endowed. This, however, has not yet been realized.

Thus was created the new department "Art as Applied to Medicine," the development of which was to be my task. The purpose is to train new generations of artists to illustrate the



medical journals and books of the future and to spare them the years of trials and disappointments of their self-taught predecessors. I can testify that a vast amount of precious time is thus lost. This school is the only one of its kind in existence. It is designed for the needs of two classes; for medical students and research workers, one afternoon a week and for art students and artists during the entire week. Hitherto the work of instruction has been followed in temporary quarters in the physiological laboratory and my own work has been done in the administration building of the hospital, and recently in the surgical building. Next year we expect to move into a permanent home in the Hunterian Laboratory, where my workroom will adjoin the students'. The character of the instruction is briefly as follows:

First. The medical students begin by making realistic charcoal studies of bones, which teach them accurate draughtsmanship and the principles of light and shadow, as a means of obtaining plastic effects. Next comes line drawing, the basis for rapid sketching. Then follows drawing of anatomical models, specimens, etc., in various techniques suitable for reproduction. Special instruction is given in microscopic drawing.

Second. The art students begin by making careful artistic studies of the skeleton, after which they dissect the human body. Every region is repeatedly drawn from various angles, then the entire body is studied and drawn again by means of frozen sections. Fresh materials from autopsies and animals are used to accustom the student to the appearance of living tissues. He injects some of these himself. Histology is now taken up in order to train the eye to appreciate the texture of tissues of all kinds. Hardened and fresh pathological material teaches the student cause and effect in disease, and makes him appreciate more minute differences in the appearance of healthy and diseased organs. The art student is now ready to understand medical and surgical clinics. He learns to sketch examinations, treatments and operations. Parallel with and supplementing these studies is instruction in all the necessary techniques, and demonstrations of the methods of reproduction.

During his two years of study the art student finds time to make several original drawings for publication. These are printed in medical journals and give the artist an introduction to the practical side of medical illustration.

Besides these two classes, I have for several years given lectures in topographical anatomy and also in artistic anatomy, but this is here irrelevant.

A large part of my time, however, is still devoted to drawing and I hope it always will be. I must say a few words concerning my own work, chiefly because the basis on which it is now done is not fully understood by those who have the right to request my aid as an illustrator. My function is to illustrate, free of charge, any important publication written by an officer or student of The Johns Hopkins Medical School. The article, however, must be already written, or I must have reasonable assurance that it will be. As many of my drawings

made during the past three and a half years have not yet been reproduced, because the paper for which they have been prepared, has not been written, it is evident that it is my duty to protect the department against such procrastination in future. If the illustrations for any one article prove to be too numerous, an art student will furnish the majority of them, while I will do only the more intricate ones. For such work, the student should be paid a moderate amount. Any single drawing of a given type made by a pupil will be free of charge, for he will consider it a part of his study. Repetitions of the same type, however, call for remuneration. Work of this character I prefer to have done after hours or during vacations. In the past it has sometimes been difficult to adjust such matters to the satisfaction of all concerned, but we hope that in the future a more perfect system may be found.

I repeat there is no charge for my work. I am paid by the university out of the fund granted for the purpose. Of course, I cannot find the time to do all the work that should be done. I must discriminate and try to determine which of several papers will prove the most important. In the past I have endeavored to divide my activity fairly equally among the various departments, using my own judgment in regard to the relative scientific and practical importance of the work. I believe it will be better in the future to relieve me of this responsibility, and, as Dr. Cullen suggests, appoint a committee, the function of which will be the selection of the papers I am to illustrate. Of all my drawings, I must request at least six reproductions printed by hand press on glazed paper. These proofs are needed in my file and in the annual report to be submitted to the donor of the fund. All my drawings remain the property of the foundation "Art as Applied to Medicine" of The Johns Hopkins Medical School. When the engraver is through with them he is expected to return them to me uninjured and in clean condition. Each drawing is numbered and stamped with directions to that effect.

The speed with which I can furnish drawings depends on the amount of time each day I am able to devote to my own work. If the number of art students is large and they happen to require considerable attention my chance of drawing is small. The nature of the art course is such that each student receives personal attention. This may require the greater part of the day, while at other times an hour or two suffices to guide the daily work and study of the whole group.

The future and its prospects can be fairly well determined by an analysis of the past and present. Assuming that the department can be put on a permanent basis financially, the following is what we may confidently expect to accomplish:

First. Through the course for medical students, we hope to establish a nucleus of artistically gifted students in each class, who by their example will stimulate the others to practice sketching and drawing during their scientific studies.

Second. Research workers will always find me ready to guide them in illustrating their own work. There is no question but that a certain type of medical illustration can be better executed by scientists than by artists. I refer here to that class of simple pictures in which the scientific element



predominates, while the artistic requirement is so slight that a few weeks of practice will render the scientist capable of making his own sketches or drawings.

Third. One of the most useful accomplishments of a physician or teacher is his ability to draw on the blackboard. This, I believe, can be acquired, and I expect to organize a class to teach medical students blackboard sketching.

Fourth. By establishing and maintaining a high artistic standard we expect to attract the best and most intelligent type of art student, for a cursory view through the literature shows that there is room for many capable medical illustrators. Most medical books are still more or less crudely illustrated, because there are yet a great number of inefficient artists engaged in the work. I receive many requests to recommend artists but am unable to do so. The demand is yet far exceeding the supply: Publishers, medical schools, research laboratories, private physicians and surgeons desire illustrators either for the purpose of making records or books. Medical progress is swift and constant and many a subject considered a closed chapter has been reopened by some discovery, thus necessitating newly illustrated books. The few artists I have trained so far have been offered positions before completing their studies.

Fifth. Our artists in the past have illustrated a large number of articles and several books. This is an advantageous arrangement for all concerned and I propose to continue and expand this branch of our activity.

Sixth. One of our most important problems at all times has been the improvement of the quality of the reproduction. Engravers as a class are not properly equipped to handle medical work, and it is to be hoped that ways and means will be found to train a group of engravers and lithographers who can be safely trusted with the etching and retouching of our cuts. It is particularly the latter art in which the present engravers are deficient. Much of our engraving is done by large concerns in other cities. An unsatisfactory cut is often returned by us with criticisms written on it, but correction of faulty work by long distance communication is impracticable. Valuable time is lost, and the corrected proof is rarely better than the first; often it is worse. Therefore, I believe that all engraving, and also printing, should be done in Baltimore, and if possible under our supervision.

Seventh. Regarding the future of my own work as an illustrator, I repeat that all my time not occupied in teaching will continue to be at the service of the Medical School, free of charge. Any important publication requiring illustration will receive my cordial cooperation. In order to guard against stagnation of style and technique, I expect to continue to experiment with new media and also to vary the type of picture whenever practicable.

It is hoped that the new quarters will afford the department the much needed space and facilities, where we can work and study without disturbance, and where I can be at hand with advice and assistance at any moment of the day.

## A BRIEF OUTLINE OF THE STATUS OF RADIUM THERAPEUTICS.

By CURTIS F. BURNAM, M. D.

Fellow alumni, it is a great pleasure to join with you in this twenty-fifth anniversary celebration of The Johns Hopkins Medical School.

The limited time at my disposal makes somewhat difficult a clear presentation even of the barest outline of the ascertained facts and questions which arise in considering the status of radium as an agent for treating diseases. Therefore, you will, I trust, pardon any glaring omissions or obscure statements. Volumes could and have indeed already been written on this many-sided subject. I shall be satisfied if I awaken your interest and stimulate you to further investigation of the radium question.

So much that is exaggerated, so much that is unscientific, so much that is absurd have appeared in both the lay and professional press of this country, that it need excite no wonder that most of you are probably in doubt as to whether radium really belongs to the armamentarium of the physician or of the quack. Some of the best-known surgeons in America have publicly gone on record with statements that radium is without any value whatever; others more guarded have stated that it is of marked value in treating superficial cancers and skin diseases, adding that its rays are practically identical with those from an X-ray tube. These opinions might be neglected,

as the authors have almost invariably had no experience with radium, except for the fact that their wide reputations give undue weight to their opinions, and bias many of our profession, who are misled into believing that such conclusions are the fruits of careful and painstaking investigations. The attitude of European medical leaders stands in sharp contrast to this opposition in America; in Germany especially the radioactive substances have been eagerly welcomed and are being painstakingly tested out by the leaders of medical and surgical thought. Practically all of those who have used radium consider it an agent of great value, and some of the most eminent men, as Doederlein in Munich, have expressed enormous enthusiasm and hope for its possible accomplishments.

Although radium has been employed in treating cancer and other diseases for more than ten years, the acute interest in it and most of the now great medical literature in regard to it have been produced during the last three years. This long latent period seems to have been much more due to scarcity of material than to the failure of those using it to secure suggestive and interesting results. For a time the only source of radium was the pitchblende deposits in the Joachimsthal Valley in Bohemia. These mines were bought from private individuals and have been operated for several years by the



Austrian Government. During the last three years radium has been produced in quantity from American, Australian, Portuguese pitchblende deposits and other minerals. In addition to the greatly increased radium production, the discovery of mesothorium by Hahn has led the Welsbach Company of Germany to produce a large amount of this substance, which has similar physical properties and is considerably cheaper than radium. The distribution of mesothorium to the medical clinics in Germany has led to very active investigations and many publications. You have but to refer to the journal, *Strahlentherapie*, now in its fifth volume, to appreciate the amount and the character of the work already accomplished.

In the United States the names of Howard A. Kelly, Robert Abbe and William Morton will always be associated with the development of radium therapeutics; they were the pioneers here and have consistently advocated its use amidst general discouragement.

My own experience has been gained through association with Dr. Kelly and extends back about eight years, when he purchased his first small amount of radium. Two years ago we added greatly to this original store and since then have continued to increase it, until to-day, and for some months we have been working with about one gram and a quarter of radium element. This is not a large amount although it relatively seems so. We have repeatedly used the entire amount for a period of 48 hours in treating a single case. At the Howard A. Kelly Hospital, where the work of Dr. Kelly, Dr. Robert Lewis and myself has been carried out, we have treated nearly 1300 cases up to the present time. Some of these are four or five years old, but most of them are of the last two years.

I should prefer for time's sake to omit all reference to the chemistry and physics of radium, but so completely does an intelligent comprehension of the medical uses of the material depend upon an elementary knowledge of its physical properties, that a brief explanation seems unavoidable.

Radium is a metallic element belonging to the strontium-barium group. It readily forms salts with the mineral acids and is the leading member of the peculiar radio-active group of elements which are characterized by atomic instability. Radium itself is formed by atomic reduction from uranium. It loses a portion of its atom to become a gas called radium emanation, and this in turn is the mother, grandmother, etc., of a series of solid elements. The so-called radium C, third in series from the emanation, is that member of the group which particularly concerns us, as it is from it that both the beta and gamma rays are derived. Radium emanation can be separated from radium as fast as it is formed. A given amount of radium is capable of producing a given amount of emanation. The emanation reaches a maximum and then disintegrates at the same rate that it is being formed. In about four days a given amount is reduced to one-half. If radium or radium emanation is sealed in a glass or a metal container it begins to produce radium C. The maximum amount of radium C is obtained in a radium preparation so

placed in a glass tube in thirty days. The maximum amount from emanation is produced in three hours and thirty minutes. Radium C itself can be isolated, but has such a short life, only two or three hours total, that it cannot be effectually used in practical treatment.

The essential characteristic of the radio-active substances is the giving off of invisible rays. These rays must not be confused with the emanation, which is an element just as radium itself is. The rays have been divided according to their physical characteristics into three kinds: the alpha, the beta and the gamma.

The alpha ray is a positively charged atom of helium. It has a very small power of penetration, being completely stopped by a thin sheet of writing paper. It acts very powerfully towards inducing chemical change in both inorganic and organic matter brought in contact with it. The beta ray is a negatively charged electrical ion which has about the velocity of light and will easily penetrate several centimeters of living tissue. It has also a marked capacity for inducing chemical changes in organic matter subjected to it. The gamma ray is not particulate matter, but a vibration of ether similar to ordinary light and to the X-ray. It differs from them in being of much shorter wave length and of much greater penetration. It has power also, but to a lesser degree than the alpha and beta rays, to produce chemical change in organic matter exposed to it. When a radium salt is inclosed in a glass tube, alpha, beta and gamma rays are produced within the container. The alpha rays are held in the tube, while the beta and gamma rays penetrate its walls, and pass out into the surrounding medium in radial lines, thus making a sphere of radiation. When the glass tube is further surrounded by 2 mm. of lead, the hardest beta rays can no longer penetrate this envelope. It is possible, therefore, in medical treatments to use all three kinds of rays together, the beta and gamma rays together, or the gamma rays alone. It is impossible to use the alpha rays alone, and it is difficult to use the beta rays alone in anything except experimental work.

From the above it is evident that radium or one of its derivatives can be used in two essentially different ways: firstly, it can be taken into the body by mouth, hypodermically or intravenously as any other soluble drug; secondly, it can be applied from either outside or inside the body in sealed tubes or other containers in the same general way that an X-ray tube is employed.

The internal use of radium or of radium emanation, which being a gas can be readily taken up through the lungs, has been principally investigated in Germany, and offers an immense field for study. There seems no question but that certain forms of gout, rheumatism, chronic arthritis and neuralgia can be greatly helped by its use. It has a pronounced effect upon the hemopoietic tissues, in small doses stimulating, and in large doses destroying them. Unquestionable improvements have followed its use in cases of pernicious anæmia, leukæmia and erythro-polycythemia; likewise in certain patients suffering with high blood-pressure, a return



to the normal with complete disappearance of subjective symptoms being frequently obtainable. Our own experiences with these perhaps properly called medical uses of radium, have been too limited to permit us to do more than to state that we have seen encouraging results in many of these conditions and that we are also favorably impressed with the reports from abroad as well as with personal interviews with nearly all the well-known investigators in this field. We believe that under the strictest diagnosis and general medical investigation, with the co-operation of an experienced radiophysicist, this form of using radium will prove a valuable adjunct to existing methods of treating disease, and that the cases suitable for it will be determined. At the present moment this is certainly not the case, for the greatest confusion obtains. The situation is comparable to what the salvarsan treatment of syphilis would be under conditions where there was no definite diagnosis possible, and where the doses of the salvarsan used varied from one one-hundredth to ten times the dose actually found efficacious to-day. Can the confusion be wondered at?

Taken internally, radium acts with all its rays on all parts of the body. When sealed in glass or metal containers and properly disposed, any part of the body can be subjected to gamma radiation, and many parts to the combined gamma and beta radiation. A given part of the body can be radiated either by placing the radium carrier on the outside or on the inside of it. It is this local radium action which has been the principal object of our investigations. Such applications of radium are for convenience sake called the surgical uses of radium.

The method of separating the gamma rays from the total rays has already been described. There are, however, two other important physical considerations that must be borne in mind: first, that as the rays are given off from a point in every direction, the intensity must of necessity vary inversely with the square of the distance; this is best exemplified by taking a tube of radium and placing it 1 mm. away from a surface to be treated, and then taking the same tube and placing it 1 inch away from the surface to be treated. In the first instance we will say that in one minute the surface immediately underneath the tube receives one unit of radiation. In the second case, to determine the amount of radiation it is necessary to square 25 mm., which is the number of millimeters in an inch. When this is done it is evident that in one minute the skin immediately underneath the tube receives only one six hundred and twenty-fifth of a unit of radiation, or, expressed in another way, the tube at 1 inch would have to be left 625 minutes to obtain a unit dose on the surface. Sticking to our example, suppose the endeavor is made to radiate tissue 1 inch below the surface with the tube in the first place 1 mm. distant, the surface would receive 625 times the dose that the tissue to be radiated would receive. On the other hand, when the tube is 1 inch away from the surface, the surface dose is only four times as great as the dose 1 inch underneath the surface. By increasing the distance from the skin, the dose at 1 inch depth can be brought nearer and

nearer to the dose given the surface. It is apparent, however, that with a given amount of radium the time must be greatly increased, or with a given time the amount of radium must be proportionately increased. The second important factor is that the tissue of the body absorbs a definite amount of the ray, and this is in proportion to its penetration. With hard rays much greater penetration is obtainable than with soft. This is well recognized in X-ray work.

The ideal aim in radiation is to apply to all parts of the diseased area or volume to be treated as equal a radiation as possible. The radium must therefore be placed in such positions with reference to the field that this is obtainable. In radiating a given area of the body and reporting results, it is essential that the type of growth, its location, its exact volume, the general condition of the patient, the amount of radium, the duration of the application and the distribution of the radiation be all clearly stated. In surface and near surface applications filters should not be dense and should allow action of the beta as well as the gamma rays. Where deep-seated regions are to be treated from the outside, owing to the absorption by the tissues of the beta rays, only gamma rays should be employed. For example, in treating skin diseases the radium is best applied in large, flat applicators directly on the surface, and in treating intra-thoracic growths, the applicator should be surrounded by at least 2 mm. of lead and placed at least 2 inches away from the skin. A deep-seated growth may be radiated from a number of different skin portals, thus bringing the dose in the interior to any desired quantity without over-treating any one spot of the surface. In addition to this distance radiation evenness of radiation is securable in the following way:

Fine, capillary glass tubes are filled with radium emanation and these containers are placed in hollow needles. It is possible to insert a number of such needles at a uniform distance from each other into the tissues to be radiated. By this means it is possible to radiate a given volume, as for instance the floor of the mouth, the tongue and neck, with an approximately uniformly equal and easily determinable beta and gamma radiation. It can readily be seen that where applicable this method is much more economical than distance radiation. Great care, however, must be taken that the exposure is not so long or intense as to cause sloughs or other injuries. It is proper to say in this connection that as yet the elementary facts are just being worked out. It is not known, for example, whether a short intense or a prolonged feeble radiation is preferable. The determination of this one point, alone will demand a tremendous material most carefully studied, and there are many others.

It is often asked, how does radium act? More than one uninitiated pathologist has stated that it acts simply as a very efficient cautery. Nothing could be further from the actual fact. While it is true that very intense radiation applied for a long period brings about complete necrosis and sloughing of tissue, nevertheless such sloughs are extremely hard to control and lead to painful wounds. As a cautery, radium is



much inferior to commoner agents. The general impression is that the advocates of radiation hold that the radiation has a selective, deleterious influence on all pathologic tissues, but does not harm normal tissues. I have been frequently asked why is it that the rays pick out only the pathologic cells and leave the healthy cells? As a matter of fact, there is a marked selective tendency in this direction. It can be assumed that radiation deleteriously affects all living tissue, but that under this injurious influence the normal tissues are preserved because the fluids and the protective agencies of the body are all constructed to help the normal tissues, and that the pathologic tissues disappear because, weakened by the radiation, they are unable to withstand the normal protective mechanisms of the body. Facts which seem to support this view are that the same kind of tumor or growth in two different individuals may react very differently under exactly similar amounts of radiation. This is as well marked in benign growths, such as uterine fibroids, as in cancer. Viewed from this standpoint it would seem that a favorable effect from radium is obtainable only in such bodies as have definite immunizing substances in their fluids and tissues. That, however, certain tumors are much more easily injured, or that much more natural resistance against them exists, is shown by the fact that certain growths disappear with slight radiation and in a large percentage of cases, while others show just the opposite tendency. Another observation indicating the importance of the body resistance is afforded by the fact that active tubercular glands will disappear in a few weeks under a radiation which has little or no effect on tubercle bacilli growing in culture outside the body. It should be borne in mind clearly, however, that certain neoplastic tissues are but little influenced by radiation, and also that there is an immense difference in the resistance of different normal tissues. Lymphatic organs are particularly sensitive to radiation and are very easily destroyed. The endothelium of blood and lymph vessels is likewise quite sensitive. After radiation it tends to swell up and occlude the lumen of the vessels. The avascularity of radiated tissues after a few months is pronounced. Cartilage, bone and ordinary connective tissue are generally very resistant. The hair follicles, the glands of the skin, the reproductive parts of the ovary and testicle are very easily injured. We might go on multiplying examples indefinitely.

Not only does the degree of change vary, but also the latent period of change. This is dependent both on the character of the radiation and the character of the tissue treated. For example, if sufficient radiation with soft beta rays is given to produce erythema of the skin, this condition will appear in a week on the average. If such an erythema is produced by hard gamma rays it may not appear until the fourth week after the radiation, or even later. Taking another example to show the difference in tissues, a radiation with gamma rays may cause the disappearance within 48 hours of a large lymphosarcoma. Equal radiation given to a carcinoma of the cervix may produce no visible change whatever in five or six days,

but nevertheless leads to the entire disappearance within five or six weeks.

It is evident that the histological changes will vary greatly with the tissues treated. Taking the cervix carcinoma as an example one finds in three or four days a tendency for the nuclei of the cells to swell and the protoplasm to become vacuolated; at the end of two weeks many of the cells are disintegrating; at the end of four weeks all carcinoma cells may have disappeared and in their place a new connective tissue formed; at the end of several months there is a great deal of connective tissue and a marked diminution in the vascularity of the part. Nerve and brain tissue are fortunately very resistant. Any injury to these tissues from radiation would seem to be due to changes in the blood-vessels supplying them.

So much for a hasty review of general principles. Now for a brief summary of clinical results and suggestions as to value.

#### RADIUM IN GYNECOLOGY.

Perhaps the most striking effect of radiation in this specialty is in its certain control of excessive uterine hemorrhage due to metropathies, or disturbed ovarian function. Every gynecologist has to deal with those women who either bleed continuously or excessively in abnormally prolonged menstrual periods. Such cases are commonest in very young girls or in women past 40, but occur at any age. In some of these cases there is formed a polypoid condition of the endometrium, in others simply a slightly enlarged hard uterus. Even the milder cases suffer from the results of anæmia, and in the severer forms the patient may actually die from hemorrhage, unless relieved by operation or by radium. While palliative operations, particularly curettage, give temporary relief, permanent relief is, as a rule, only obtained by hysterectomy. The use of radium offers a far simpler and safer procedure. Usually a single application of 300 mg. for three hours intra-uterine causes a permanent amenorrhea. A second application can be given in six weeks if the first fails in the desired result. These patients pick up rapidly generally, suffer no inconvenience and are usually, in more than 50 per cent of the cases, free from hot flushings or other menopausal symptoms. In very young women the treatment is greatly shortened, with the result that menstruation is rendered normal in type so far as duration and loss of blood are concerned. It is only the very occasional case that has to be treated to complete amenorrhea to secure a perfect restoration to health.

Hemorrhage associated with fibroid tumors of the uterus is likewise and in the same way readily controllable, and in addition the tumor itself will either completely disappear or be reduced to an insignificant size. About five per cent of the cases treated do not decrease in size. Some of these are calcified fibroids and in others the patient lacks the necessary solvents in her blood. Neither the size nor the position of the tumor are of moment. The rate of disappearance varies greatly. After a single radiation one tumor may disappear in two months; another only after six or eight months. In some cases large uterine fibroids disappear without any effect



on the periodic, normal recurrence of menstruation. Tumors in women past the menopause also readily go down. This treatment is without danger, it is usually accomplished in a single radiation, and is in our opinion the procedure of choice. Operation should be limited to fibroids complicated by other pelvic conditions and to those which do not yield to the radium treatment.

Foreign observers report successful results in cancer of the body of the uterus. We have seen large, recurrent, abdominal, metastases of this type of cancer go down rapidly, but no cases were cured. The results of operation are so good, and the difficulties of determining the extent of the cancer so great, that as yet we have not tried radium in a single operable case, nor would we advise its use in any person except where some general complication precluded operative interference.

In cancer of the cervix uteri and of the vagina most remarkable results are possible. The hard, scirrhus cancer of the cervix is the most resistant type, and the cellular, slow growing medullary carcinoma, especially that which tends to spread over the vaginal wall, is the most favorable. It is easily possible to radiate away metastases in the vagina, bladder and rectum, without interference with the integrity of these viscera. A huge, inoperable carcinoma fixed to either pelvic wall can within a few weeks appear clinically healed, and some of these patients stay healed for at least several years. Where healing does not occur there is almost invariably improvement in the general condition, bleeding and discharge cease, and pain is diminished or disappears. We have seen not only the parametria clear up, but also regional lymph glands. There can be no question that radium is a great boon to patients suffering with inoperable and recurrent cancer of the cervix uteri. It is equally certain that its use in operable cases, along with operation, will greatly increase the number of permanent cures. It is still uncertain whether operable cases should be treated with radium alone. It seems likely that there are curable cases from operative treatment which would resist radiation, owing to a lack of protective resistance in the patient's own body. In the future, much greater care must be exercised in reporting cancer results. Great detail must be given as to the type of growth, its method of extension, its actual extent, etc. It may develop under such criteria that those cases which resist radiation also become general from their very incipency. For the present it seems sound advice to follow out both treatments, and to limit the radiation alone to those patients who have some general contra-indication to operation.

The fourth class of patients who are unusually benefited by the treatment are the pruritus and kraurosis vulvæ sufferers. It is truly astonishing in these patients to see the itching disappear and the skin return to normal. Usually two or three mild applications suffice to bring about this result.

Ovarian tumors, tumors of the vulva and the other gynecological conditions have given much less satisfactory results, and our results are not at present in a position to be reported upon.

#### RADIUM IN GENITO-URINARY DISEASE.

The papilloma and papillary carcinoma of the bladder are favorable tumors, although the amount of radiation has to be greater than in the cervical carcinoma. The squamous-celled cancer of the bladder is very resistant; tubercular ulcers and other chronic ulcers are quite favorably influenced. We have under observation several patients with simple hypertrophy of the prostate gland, who seem to be greatly improved by the radium treatment. We have also one case of prostatic carcinoma apparently cured. It would seem that the conditions of the prostate offer an extensive and promising field for the trial of radium radiation. Comparatively little is at hand in the foreign literature in regard to these patients.

#### RADIUM IN RECTAL DISEASE.

Adenocarcinoma, especially that just above the sphincter region, is definitely curable in some cases and beneficially influenced in almost all. The squamous-celled cancer of the anus is much less readily influenced. Multiple polyposis does remarkably well. In both the rectal and vesical cases radiation treatment is indicated in the early stages when the operation means serious mutilation. If it fails, operation can be resorted to. In operative cases, both the permanency and the percentage of cure will be increased by a combined treatment. Some inoperable cases are undoubtedly curable.

#### RADIUM IN ABDOMINAL TUMORS.

The most striking results are obtainable in the retroperitoneal sarcomata. We have some immense growths of this type which have completely disappeared, and a few which have been free from recurrence for months. The colloid carcinoma of the intestine does not do so well as that of the thyroid gland, but nevertheless is a condition in which radium treatment offers great hope. Several cases have been clinically well over long periods. We have had no definite cures in stomach or liver carcinoma, having seen only very advanced cases. Werner of Heidelberg, *Strahlentherapie*, vol. 5, part 1, p. 10, reports several cures. This important field has just been touched. It would seem that an intelligent combination of surgical and radiation treatments might lead to a very great improvement in the present methods of treatment. It is of interest that ascites due to abdominal cancer is occasionally completely done away with by radiation. Among unusual conditions we have observed in a girl the complete disappearance of a sarcoma of the left kidney. In a man with a hæmoglobin of 120, marked cyanosis, difficulty in breathing and an immense spleen, a thorough radiation of the spleen has resulted in a return to normal of the blood and spleen, and apparent perfect health, which has persisted for several months.

#### RADIUM IN THORACIC TUMORS.

Werner, *loc. cit.*, as well as N. S. Finzi, *Radium Therapeutics*, 1913, report healed carcinomata of the œsophagus. In four or five cases we have not succeeded in obtaining a





FIG. 1.—Sarcoma of the mediastinum before treatment.

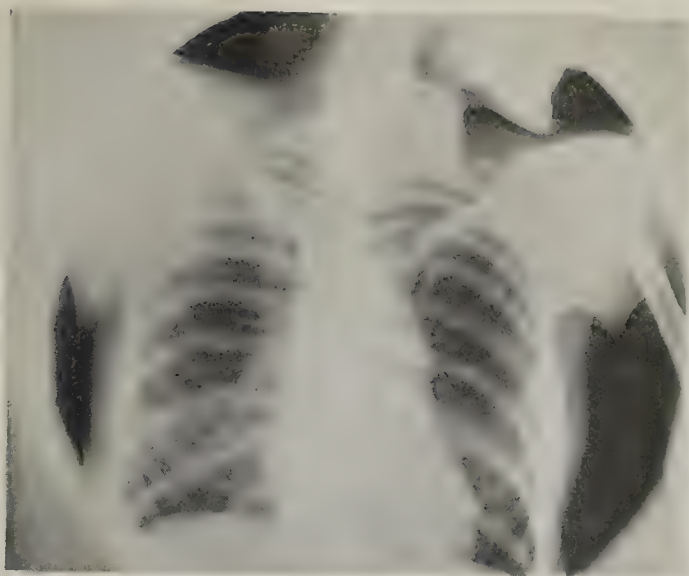


FIG. 2.—Sarcoma of the mediastinum after treatment.

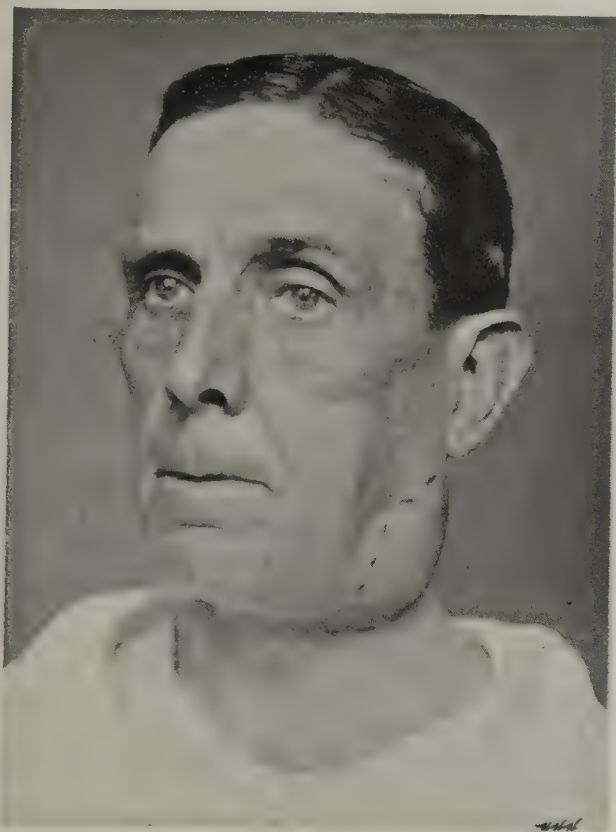


FIG. 3.—Sarcoma of the naso-pharynx, mouth and glands of neck before treatment.

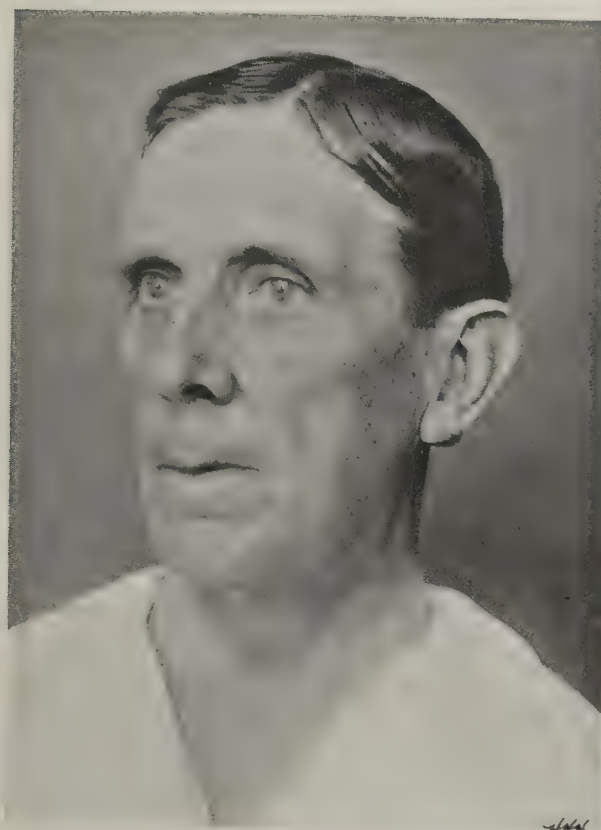


FIG. 4.—Sarcoma of the naso-pharynx, mouth and glands of neck after treatment.

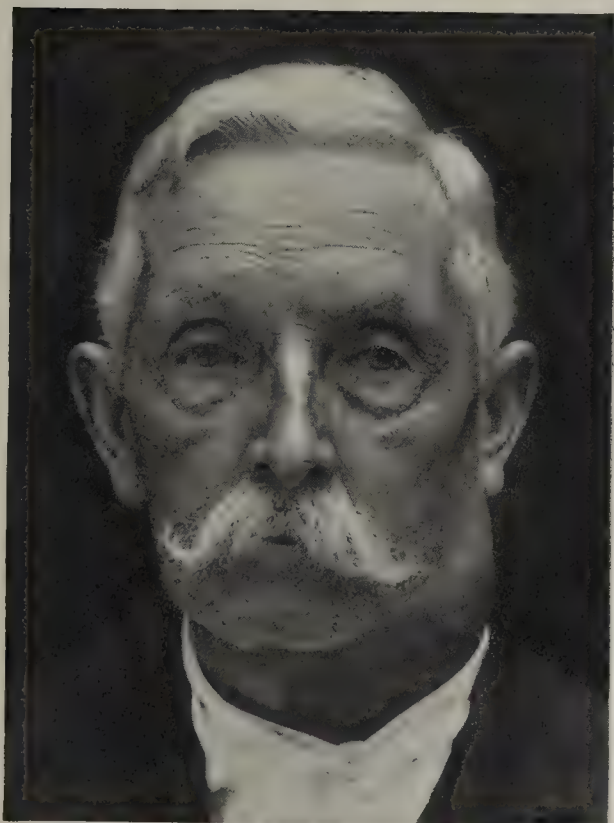


FIG. 5.—Sarcoma of neck before treatment.

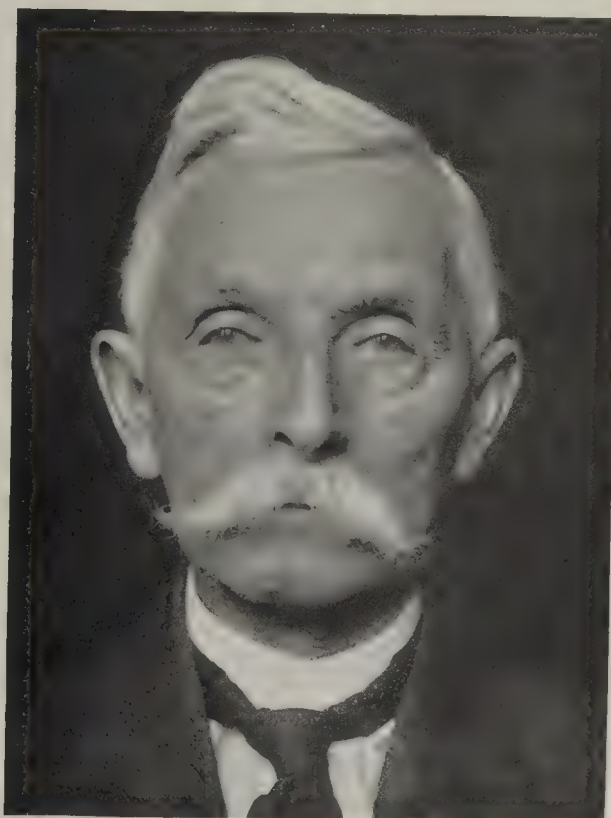


FIG. 6.—Sarcoma of neck after treatment.



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single cure so far, although there has been some benefit in most of them. Several large, mediastinal tumors have disappeared completely. One of these is illustrated in the case of Mrs. R. L., age 30, who had a large mass filling the mediastinum, extending into the neck and into the left plural cavity. Her general condition was good except for a little dyspnoea. A small piece of tissue removed from the neck showed that the tumor was a small round cell sarcoma. Under treatments given in July and August, 1913, the growth began rapidly to disappear and had entirely gone in two months. This condition has now lasted more than a year and is well shown in the skiagrams of the chest, Figs. 1 and 2, the first of which was taken before radiation, and the second six months later. A third plate recently obtained shows the same condition as in Fig. 2.

#### RADIUM IN TUMORS OF THE BREAST.

The malignant tumors of the breast are in general sensitive to radiation. This is especially true of the softer and more voluminous types. Not only do the primary growths yield, but also the axillary and supra-clavicular gland metastases. In patients with mediastinal and lung involvement, radiation is contraindicated. We have a number of patients apparently well of local recurrences after operation, where thorough radiation has been given. It is our impression that operable breast cases should have the combined treatment; that inoperable and recurrent cases should be given radium radiation as long as the trouble remains regional. It will take a long period of observation and study to definitely give radium its value in the treatment of malignant tumors of the breast, but there is certainly good evidence that it is a valuable adjuvant to our existing measures of treatment.

#### CONDITIONS OF THE THYROID GLAND.

Large colloid goiters frequently, rapidly and almost completely regress. Colloid carcinoma of the thyroid gland is a very favorable growth. We have one very extensive recurrent case apparently cured. Exophthalmic goiter, especially where there is thymus involvement, we have improved almost invariably, but as yet have not obtained a definite cure such as is obtained by thyroidectomy in many cases. Dr. Robert Abbe has reported favorable cases belonging to this group. We feel that with careful investigation and working out of proper techniques there is an extensive field for trial of radium in treating disorders of the thyroid gland. It should always be tried in thyroid malignancy, either alone or as an adjunct to operation.

#### CONDITIONS OF THE LARYNX.

There is reasonable ground for believing that tubercular ulceration of the larynx can be greatly benefited by radiation. The percentage of carcinomata, especially those belonging to the papillary and basal-celled types, that can be cured is fairly large. We have three cases well for more than a year, and several others well for shorter periods. These patients have

been treated almost exclusively by radiation from the outside. Considering the usual hopelessness of these patients radium seems to be of great value here, competing most favorably with the mutilating laryngectomy.

#### RADIUM IN TONSILLAR DISEASE.

The basal-celled epithelioma and the sarcomata are unusually favorable, even when they have extended to the glands of the neck. As these cases are incurable surgically, we feel that the small group of apparently cured cases is a real triumph. The spinous-celled carcinoma of the tonsil is unfavorable, but can be helped and cured in some cases. In this tumor the burying technique is extremely valuable.

#### RADIUM IN MUCOUS MEMBRANE OF THE MOUTH.

With the exception of the lip epitheliomata, the mucous membrane cancers of the mouth are harder to deal with than similar growths on the skin. The tongue cases are particularly difficult and disappointing. Wherever possible in these growths, which are mostly spinous-celled epitheliomata, the radium should be used in conjunction with surgical treatment.

#### CONDITIONS OF THE NASO-PHARYNX.

The tumors of the naso-pharynx are many of them sarcomata and are practically all incurable, but yield to radium a most gratifying field. It is truly astonishing to see how some of these immense growths clear up and seem to remain well. Figs. 3 and 4 are photographs of a patient admitted in the hospital on May 23, 1914, with an immense tumor filling the naso-pharynx and extending into the glands of the neck on both sides. When first seen he could not speak, and could hardly swallow because the tumor pressed the palate down against the teeth. Tissue removed showed round-celled sarcoma. The patient was immediately radiated and by June 2 the tumor had entirely disappeared. This man has remained well ever since. This patient is typical of a considerable number whom we have had opportunity to consider and treat.

#### CONDITIONS OF THE NECK.

The primary sarcomata, particularly the small round-celled and angio-types, do extraordinarily well. It is very common to see the complete disappearance of a large tumor after a single thorough radiation, such as is shown in Figs. 5 and 6. The first of these photographs represents conditions prior to operation, and the second those found after the radium treatment. It is also of interest that this patient, who became clinically well in two weeks, has remained so for nearly 18 months. The metastatic cancers do not do very well in most cases. Hodgkin's disease and tubercular glands are both most favorably influenced. Our experience to date indicates that in the susceptible sarcomata radiation alone is preferable to operation or to operation and radiation. In the unsuceptible sarcomata and carcinomata operative and radium treatment should be combined wherever possible.



## CONDITIONS OF THE SKIN.

Skin sarcomata, including the melanotic form, are quite susceptible to radiation. The basal-celled epitheliomata of the rodent ulcer type respond well in a large percentage of cases, even when very extensive. The spinous-celled epitheliomata are much more resistant. In this class it would seem wise, as in any epithelioma which is resistant, to combine the radiation with surgical procedure. The inoperable cases, however, are an exception, except where the actual cautery and radium can co-operate. It is most important in these patients not to be satisfied with an apparent cure, but to keep under observation and re-radiate for at least two years. Among non-malignant skin diseases there is the greatest variety which can be helped; birthmarks of the port wine type, of the angiomatic type, of the pigmented and hairy mole type, acne rosaceæ, lupus erythematosus, rhynophyma, lupus vulgaris, macrocheilia, macroglossia, offer peculiarly favorable conditions.

## GENERAL CONCLUSIONS.

The statements included in this paper are founded on personal observations. I have made no attempt to take results from other observers. My aim has been to enlist your interest and to point out that radium has a wide field of usefulness, the boundaries of which have not been fixed and can only be determined by long, painstaking statistical studies. We do not believe that radium has any field absolutely to itself. It is merely an extraordinarily, widely applicable, therapeutic agent, which must be used intelligently in connection with all other known methods of treatment. In connection with the treatment of benign growths it would seem that owing to its mildness and lack of danger it might be tried as a preliminary, and surgery reserved for the cases it fails in. With malignant growths, where surgery offers hope, the two methods had best be combined. With malignant growths which are in-

operable, hope is held out by the radium treatment, and especially is this true in many sarcoma cases. It is our opinion that in certain types of sarcomata which have not proved curable by surgery, even in the earlier stages, the radium treatment should be used alone even when the growth is very small. The radium treatment is also of great advantage in operable cases of malignant growth where the operation means great disfigurement and mutilation. Examples are furnished by the epitheliomata about the eyes, on the nose, the rectal and vesical sphincters, etc. While it is also probable that even in the earlier stages, where the body resistance of the patient is at its best, that no one type of tumor is curable in all cases and some in only a small percentage of cases, it does not mean that this condition of affairs need permanently exist. Better methods of radiation ought to greatly improve results, but what seems even more important is work to determine the cause of the difference in resistance in individuals and if possible to develop methods of increasing this resistance. It would seem that all the vaccines, serums and specific drugs which have been brought out in the last decade as agents for treating cancer, and many of which have apparently given results in a few cases, will have to be tried over again in combination with radiation. It is also most important that careful, comparative investigations with the X-ray be carried out, and the degree of overlapping, with the possibilities of uniting the two methods be determined. The possibilities of using the X-ray as a therapeutic agent have been tremendously increased through the technical developments of the last few years. It is possible now to give a uniform dose with the X-ray and it is also true that the character of the X-ray, so far as its penetration is concerned, is steadily approaching that of the gamma ray of radium. The surgical uses of radium embrace a field much wider than that of the treatment of neoplasms. The effects on secretory glands, on neuralgias, on local tubercular and other conditions, must be borne in mind. It is also evident that the medical uses of this drug may be considerable.

## ULTIMATE RESULTS SECURED FROM SURGICAL INTERVENTION IN SIMPLE CASES OF CHOLELITHIASIS AND IN CHOLELITHIASIS DISCOVERED DURING OPERATIONS FOR OTHER CONDITIONS.<sup>1</sup>

By JOHN G. CLARK, M. D.,

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The first American gynecologist to suggest and carry into routine practice the examination of the upper abdominal organs, during the course of a pelvic operation requiring an abdominal incision, was Dr. Howard A. Kelly. This plan was advocated by him at least 15 to 18 years ago. It is especially fitting, therefore, that the results of this practice as executed by one of his students should be recorded among the proceedings of this Twenty-fifth Anniversary of the active work of

<sup>1</sup> Reprinted with additions from the American Journal of the Medical Sciences, November, 1914, No. 5, Vol. CXLVIII, p. 625.

The Johns Hopkins Hospital. To be efficient as a gynecologist, one must be well trained in general abdominal surgery, for there are so many lesions of other abdominal organs that may exist coincident with the diseases of women that it is hazardous to attempt the surgical remedy of one without being capable of meeting in the best technical way all other pathological conditions that may be coincidentally encountered.

This general training broadens very markedly the comprehension of the gynecologist and frees him from the danger of reducing all abdominal symptoms to a pelvic basis for their



explanation. With the progressive expansion of this specialty, the discussion of reflex pains referred to the gastrointestinal system has decreased in an inverse ratio.

There existed until within the last decade a widely prevalent view, borne out by the text-books of the time, that gall-stones could be present for prolonged periods without causing any manifest disturbance of the biliary or gastric physiology. This presumption was based upon a fallacious interpretation of the symptoms. That cholelithiasis, or even a marked cholecystitis, may exist without presenting the so-called classic symptoms is no longer questionable. Modern surgery has shed much light upon this subject and symptoms that were formerly regarded as essential for the establishment of a diagnosis of cholelithiasis are now looked upon as terminal rather than initial indications of biliary disorders.

At a meeting of the American Gynecological Society held in Boston a decade ago I reported several cases of cholelithiasis associated with gynecological lesions. From a summary of the views expressed at that time I quote the following:

1. The usual statement that 95 per cent of gall-stones produce no symptoms is fallacious, because it is based on autopsy and dissecting-room statistics.
2. Bile possesses no bactericidal properties, for in the majority of cases of cholelithiasis microorganisms of a more or less pathogenic nature are discovered.
3. Under these circumstances many vague symptoms, usually attributed to gastrointestinal or general constitutional disturbance, may arise as the result of toxins elaborated about these foreign bodies in the gall-bladder.
4. All clinicians admit that a wide hiatus exists in the clinical symptoms between the early formation of gall-stones and the so-called classic attacks of biliary colic with jaundice.
5. Abdominal surgeons should carefully record all gastrointestinal or hepatic symptoms, and any other vague epigastric pains, and these should be associated with the findings secured on examination of the gall-bladder, with a view to establishing a further link in the symptomatology of cholelithiasis.
6. As cholelithotomy has been attended, in a large series of cases, with a mortality of less than 2 per cent, the removal of gall-stones during the performance of some other abdominal operation is not too hazardous an undertaking.
7. This coincident operation should be undertaken only as the result of most careful surgical judgment, for if the patient is in a critical condition from a prolonged operation, or if the primary operation has been done for a septic condition, this additional operative procedure may be attended by serious consequences.

That the interpretation as expressed at that time has been sustained by later findings I believe the accompanying report of 159 gall-stone cases will amply prove. Since that time I have made an even more careful study of the symptomatology of cholelithiasis, and in only a small percentage of coincidental cases were these foreign bodies found to be innocuous.

In a paper recently published under the title of "Innocent Gall-stones a Myth," William Mayo says:

Ten years ago we heard a great deal about "innocent" gall-stones, which meant that gall-stones existed without symptoms, and that their presence was not suspected until postmortem examination brought them to light. We cannot now escape the conviction that the gall-stones did cause symptoms, and that we, as diagnosticians, and not the gall-stones, were "innocent."

The late Dr. Richardson, in one of his last papers, entitled "The Diagnosis and Prognosis of Gall-stone Disease from the View-point of the Surgeon," takes up the symptomatology of cholelithiasis, and shows conclusively that in many cases there is no pathognomonic group of symptoms, but that the functional derangement incident to the presence of these foreign bodies may range from vague distress to the intense, cramp-like pain which the internist is so prone to call "gastralgia." This gastralgia in itself should be regarded as a "myth." The high-sounding term may satisfy the layman, but certainly gastralgia is an infrequent symptom, exhibiting no tangible mechanical defects, and therefore it is most misleading and meaningless to both patient and physician.

Richardson expresses the view that these so-called innocent cases should be treated before they manifest the positive symptoms that indicate that an advanced stage of pathological change has taken place in the biliary system. In his expressive style he says:

Shall we wait for pathological changes of serious disease to become so characteristic that diagnosis is unmistakable? Shall the trend of medical and surgical thought be toward accuracy at the expense of safety? Shall the disease come to the surgeon or the surgeon go to the disease? Shall the lesion prevail until the surgeon, perforce, strikes a blow, or shall the surgeon assault, overwhelm, and destroy the lesion at its very inception? Shall we take that initiative so important and so favorable in matters of war, or shall we rest on the defensive?

The answer is simple it seems to me. With our utmost endeavor we must make our attack at the earliest possible moment, after we have, with reasonable accuracy, located the enemy and ascertained his resources.

This, then, is the viewpoint of the surgeon. Now what of the physician? Their views are divided between a conservative medical and an active surgical intervention. In general, however, many excellent practitioners still exhibit a tendency to delay surgical intervention until the classic attacks set in. Too many are still dominated by the statistics of almshouses and hold to the now largely discredited belief as to the innocuousness of gall-stones.

In a Mütter Lecture on "Infection of the Biliary Tract," delivered in 1906 before the College of Physicians, the late A. O. J. Kelly, one of the most brilliant of the younger physicians of this country, very judiciously discussed this entire question, and unhesitatingly commended the wisdom of early intervention in these cases. I quote two paragraphs from this lecture, which will tend to show the general trend of his views concerning the dangers of cholelithiasis and the results of surgical treatment. He says: "Between the extreme of innocuousness or comparative innocuousness and quick and early disaster lie the great majority of cases of biliary infection." In discussing possible failure after surgical intervention he remarks: "The fact that the operative results are not always what were hoped for is not in itself a contra-indication to operation; on the contrary, these untoward results are often attributable rather to the fact that in many long-delayed cases the anatomical lesions are such as to be almost, if not quite, irremediable by any and all means at our command."



THE AFTER-HISTORY OF CASES.—Surgeons during the last few years have modified many old and devised countless new operations and the immediate results of these procedures have been widely studied. The ultimate results in cancer operations have been accurately traced, and in other diseases we have ascertained the percentage possibilities of cures; in many, however, no accurate statistics as to the remote results of surgical intervention have been secured. In conjunction with my assistant, Dr. Block, I have traced with great interest the results of a very large proportion of our cases of gall-stone operations, and have set down here in tabular form our findings. In one group are included cases in which an operation was performed for cholelithiasis without any associated gynecological condition. In the second group we have placed those cases in which gall-stones were discovered during a gynecological or other abdominal operation.

Of our series of 160 cases, in only 14 per cent did we fail to secure accurate information as to the outcome. No case has been included in this list that was operated upon less than nine months previously.

*Type of Operation.* In our earlier practice it was our custom to suture the gall-bladder to the peritoneum of the anterior abdominal wall, thus shutting it off from the general peritoneal cavity. After considerable experience we discovered that in these cases biliary fistulas frequently healed slowly, and patients often complained of dragging or pulling pain at the site of the attachment for some time after their leaving the hospital. This method was, therefore, abandoned and now we use instead an improvised drainage-tube, which can be sutured securely into the gall-bladder. When this is done, the gall-bladder falls back into its normal position, and is not held in a constrained position against the abdominal wall. Since adopting this plan we have observed a marked improvement in the results, as shown by the prompt closure of the drainage tract and the subsequent comfort of the patient. By this means, too, perfect drainage has been secured and in those cases in which there has been persistent postoperative nausea the tube has served to facilitate the introduction, in a reverse way, of normal saline solution into the duodenum, as was recommended by McArthur. In all cases in which nausea persists after 24 hours we attach a saline reservoir to the drainage-tube, and under one foot of hydraulic pressure permit the fluid to drop slowly into the gall-bladder. Great care must be observed to avoid the slightest excess of pressure, which might induce a rupture about the point of insertion of the tube in the gall-bladder.

In our series of cases the drainage was usually maintained for ten days. This rule is, however, an arbitrary one, and in some cases the drainage period may be extended.

Within the last two years we have resorted to cholecystectomy in a greater proportion of cases, for experience has shown that if the wall of the gall-bladder is thick and indurated; or if it is dilated and very thin; or on inspection of the interior of the organ the mucosa is found to be eroded or exhibits a strawberry mottling, cholecystectomy is the operation of choice. In those cases in which there are few or no symptoms,

we have found that the removal of gall-stones with a ten days' drainage is followed by complete recovery and that there are no postoperative sequelæ. When, on the other hand, the gall-stones have caused more or less extensive pathological changes the outcome, so far as complete recovery is concerned, may be very unsatisfactory. Under such circumstances the patient continues to complain, and subsequent removal of the gall-bladder may be necessary.

From a study of the after-histories of these cases we are convinced of the necessity for resorting more frequently to cholecystectomy. Occasionally we have closed the gall-bladder after the removal of uncomplicated gall-stones, but we prefer to use a simple drain, thus obviating all danger of rupture of the gall-bladder and escape of bile into the peritoneal cavity.

From a review of this series of cases we conclude that:

1. Simple drainage is all that is necessary in cases of cholelithiasis in which there are no symptoms attributable to the presence of the stones.

2. When the gall-bladder is thickened or greatly dilated, or if it is the seat of the so-called "strawberry change," as described by Moynihan, cholecystectomy should be the operation of choice.

Through this analytical study of cases we have gained greatly in our knowledge of the best methods of dealing with the various lesions incident to gall-stones. Certainly mere drainage does not, as we formerly believed, cure every case of cholecystitis.

AS TO SO-CALLED REFLEX "GASTRALGIA," "INDIGESTION," AND "DYSPEPSIA." These terms are given prominence here in the hope that they will serve as a target for immediate demolition. In our series of cases many patients were referred to the gynecological wards for the repair of a lacerated cervix or perineum, or for the correction of a retroversion of the uterus, who exhibited clearly defined symptoms referable to the upper abdomen; and yet were considered by the family physician as reflex manifestations, although an accurately traced history would have left no doubt as to their true significance. I am a pronounced pessimist as regards the belief that reflex symptoms in the upper abdomen emanate from gynecological lesions. In our teaching we constantly lay stress upon this point: "Locate your symptoms anatomically and then seek for the lesion in that locality." If this quest fails, then one may extend the diagnostic excursion to immediate or more remote organs.

In a very interesting case that came under our care recently the patient had suffered three years previously from characteristic attacks of gall-stone colic. A cervical laceration, which was considered to be the reflex source of these attacks, had been repaired in a suburban hospital, the patient having been kept in bed for three weeks. The recovery was prompt and the cure apparently complete. All symptoms in the upper abdomen ceased—a triumph for this antiquated doctrine. A second baby was born and this was followed by a prompt return of the old symptoms. A small laceration had again occurred, and the patient's physician referred her to the gynecological department for relief of the condition by repair of



the trivial laceration. Both physician and patient objected strenuously to even an exploration of the gall-bladder, and only when we refused to proceed with the operation without their permission was the request to explore acceded to. As a result, 200 stones were found in the gall-bladder. Following the first operation the period of rest in bed had evidently brought about a quiescence of the gall-bladder symptoms, and only after the second pregnancy did they again become active. Many similar cases have occurred in our practice.

Latent gall-stones frequently become active subsequent to parturition. This is due, I believe, to the lessening of intra-abdominal pressure, with sagging of the gall-bladder and liver, thus causing a stagnation of bile, and precipitating an attack of cholecystitis. As a much larger percentage of gall-stones occur in child-bearing women than in those who have never been pregnant, and also because a larger percentage occur in women than in men, the gynecologist should be specially alert in studying the symptoms incident to disease of the organs of the upper abdomen. Serious error is especially likely to lurk within the shadow of a reflex doctrine, casting grave discredit upon the science of gynecology.

In gynecological cases manifesting coincident symptoms in the upper abdomen the gall-bladder, by far more frequently than any other organ, is the seat of disease. In a vastly larger series of gynecological cases gastric or duodenal ulcers or gastric carcinoma have been found so infrequently as to be regarded as almost negligible. Therefore, when the upper abdominal symptoms are vague, and the possibility of diseases of the pylorus, duodenum, and gall-bladder is considered, the ratio of incidence is greatly in favor of the gall-bladder as the seat of the trouble. In our own cases the ratio is at least 100 to 1. In doubtful cases the diagnosis should invariably be cholelithiasis or cholecystitis, with the possibility of some one of these other lesions far in the background.

When should gall-stones be removed as an incidental part of a gynecological operation? We still adhere to the precautions laid down ten years ago, namely, that the coincident operation should be performed only as the result of careful surgical judgment, for, as stated previously, if the patient is in a critical condition from a prolonged operation, or if the primary operation has been a septic one, this additional surgical procedure may be attended by serious results.

Our series does not include a case in which stones were removed or even searched for if a septic focus existed in the pelvis. In every instance in which there is a record of a coincident operation for gall-stones having been performed in an inflammatory condition, this was done when the chronic stage had been reached and all activity had disappeared. A coincident operation is never performed in a purulent case even if there are decided symptoms of cholelithiasis.

In estimating the immediate and remote results of these combined operations, we have arranged our cases under three separate headings: First, simple gall-bladder cases, *i. e.*, those in which the surgical treatment was directed solely to the relief of the cholelithiasis; second, those cases in which some pelvic operation was performed and gall-stones were

accidentally discovered; and third, gynecological cases in which there were unmistakable symptoms of associated gall-bladder disturbance.

So far as the immediate mortality is concerned, the first group, consisting of 55 cases, was attended by an immediate mortality of 4.3 per cent; the second, by 7 per cent; and in the third no fatality occurred.

As would naturally be expected, the possibility of wound infection is proportionately greater when two or more operations are performed: First, because of the greater number of surgical incisions, which, of course, increase the risk, and second, the greater hazard, in changing from one operation to another, of possible defects in technique. To overcome these dangers, separate sets of instruments and rubber gloves should be employed in each new operation. So far as the instruments are concerned, there is nothing fraught with so much danger as the repeated use of the surgical needle. In a simple hysterectomy, for example, a needle used in closing the uterine stump should be discarded, for there is always danger of it becoming contaminated from passage through the cervical canal; if this has occurred, it may, if used again, infect a fresh wound.

In these combined operations the greatest care should be observed in changing from one operative field to another. We never employ in the pelvic zone any of the instruments used in a plastic operation and the same precaution should be observed in the performance of a third operation in the upper abdomen.

Notwithstanding these precautions, our series of combined operations has shown a higher percentage of wound infections than the simple gall-bladder operations, in which the percentage of wound infections was 5.9; in the combined operations the rate was 9.7 per cent in one series and 9 per cent in the other. These figures cover any degree of wound infection from a small point to an extensive break in the wound. Another point to remember is that the greater the length of time consumed in these operations the more likely to arise are untoward complications during convalescence. Thus postoperative vomiting and phlebitis are observed in larger degree in the combined operations. Pneumonia occurred only once in the entire series of cases.

In these days when hospital efficiency is arousing so much agitation, the number of days a patient spends in a hospital must be accounted for. In some hospitals the tendency has been to hasten convalescence, or, rather, to expedite the discharge of patients from the hospital. The test of efficiency should be the ultimate result secured, and not the brevity of sojourn in the hospital. I believe that a too early discharge of a debilitated or greatly enfeebled patient may lead to utter failure so far as the ultimate recovery is concerned. In free wards the personal equation must be most carefully estimated. In the case of a farmer's sturdy wife rapid convalescence may ensue after an early return home; in another instance if the patient lives in cramped quarters where the ventilation is poor and the food wretched, to hurry her home is to bring the final results in jeopardy.



In convalescence after surgical operations we have found the so-called neurasthenia to occur chiefly at the two extremes of the social scale—the pampered rich and the sorely impoverished. In the latter case the patient may never rise above the wretched environment unless she is well on the road to convalescence before she is discharged from the hospital. Further, we hold that no patient should be permitted to return to her home who possesses any disabling surgical complication. The psychic handicap to such a woman may frequently be quite insuperable. In cases of cholelithiasis we prefer, if possible, to keep our patients in the hospital until the fistula is closed, especially if they are not to be under our supervision after they leave the institution. In general, under the plan we now pursue, from 18 to 21 days is the usual length of time these patients remain in the hospital.

The causes of death in our cases were as follows:

- CASE I.—Cholangitis, which was produced by stones blocking the hepatic radicles in the liver substance, and pancreatitis, produced by a calculus that had ulcerated its way into the pancreas from the common duct. This stone was not discovered at the operation.
- CASE II.—Extensive cystic destruction of the pancreas with chronic cholecystitis, death occurring from cholemia 17 days later.
- CASE III.—Umbilical hernia and chronic cholecystitis, death occurring from cholemia five days after operation. The output of bile steadily diminished, until it finally ceased entirely.
- CASE IV.—Advanced pancreatitis with cholelithiasis, death from cholemia 19 days after operation.
- CASE V.—Cholecystitis, probable leakage about gall-bladder drain, death from a subphrenic abscess 31 days later.
- CASE VI.—Chronic metritis with densely adherent tubes and ovaries, Lane's kink, concretion in appendix, and cholelithiasis. Hysterectomy, release of Lane's kink, appendectomy, and cholelithotomy were done. Death occurred from peritonitis five days later.

In summing up these cases we observe that four of the cases died from the destructive results of advanced cholelithiasis. In only two could death be attributed to any defect in the operative technique. In one there was a leakage with the formation of a subphrenic abscess; in the other a peritonitis. It is possible that these two deaths might have been avoided.

The point that the first four fatalities should drive home is that when pancreatitis of a chronic type supervenes the biliary condition sinks into insignificance beside the grave dangers that threaten from this sequel. In these cases the surgical mortality is extremely high. In none of the combined operations in which there were no symptoms attributable to gall-stones did a fatality occur.

ULTIMATE RESULTS.—A. *Cases of Cholelithiasis Unassociated with Other Abdominal or Gynecological Lesions.* Of our series of 55 gall-stone operations not associated with other gynecological or abdominal conditions, 90 per cent of results were traced. No case returned for a second operation, and none had been operated upon elsewhere.

Of this number 69.5 per cent were cured, 15.2 per cent were greatly improved, and 2.1 per cent were not improved. Of

the entire number, 8.6 per cent died after leaving the hospital from extraneous conditions not connected with the surgical operation.

B. *Cases of Cholelithiasis with Symptoms Associated with Other Abdominal or Gynecological Lesions (77 cases).* Of this number, 78 per cent were traced; 59.7 per cent were cured, 17.5 per cent were greatly improved, 1.7 per cent were slightly improved, and 8.7 per cent were unimproved. Since leaving the hospital, 3.5 per cent died of intercurrent diseases not connected with the biliary operation.

C. *Cases of Cholelithiasis without Assignable Symptoms, Associated with Other Abdominal or Gynecological Conditions (31 cases).* Of this number 86 per cent were traced, 64 per cent were cured, 16 per cent were greatly improved, 4 per cent were slightly improved, and 8 per cent (2 cases—both excessively neurotic) were worse than they had been before operation.

It is specially noteworthy that in the second class of cases, where there were unquestionable symptoms of diseases of the upper abdominal organs, in 13 there were visible changes in the appendices, ranging from mild to acute inflammations. Thus the error in diagnosis falls chiefly between appendicitis and cholecystitis. In several of these cases the condition of the appendix gave rise to the acute symptoms which had precipitated the operation.

From this analysis we learn that the worst results occur among the combined cases in which there are manifest symptoms due to biliary changes. The ratio of the cures is in direct proportion to the severity of the symptoms. The weight of

TABLE I.—COMBINED OPERATIONS WITH GALL-BLADDER SYMPTOMS.

By FRANK B. BLOCK, M.D.

	No. of patients.	Days in hospital.	Convalescence.	Returned for second operation.	Cures.	Great improvement.	Slight improvement.	Unimproved.	Worse.	Death.
Displacement.	25	29	Vomiting, 1 Phlebitis, 1 Infection, 2	2	10	2	1	2	0	4; 2 incident to operation.
Appendix.....	13	29	Vomiting, 1 Phlebitis, 1 Infection, 1	3	6	1	0	3	0	0
Fibroid.....	12	32	Infection, 3 Pneum'ia, 1	1	9	3	0	0	0	0
Pelvic inflam- mation.....	9	27	.....	0	3	2	0	0	0	1 (peritonitis).
Ovarian cyst.	7	28	.....	1	3	0	0	0	0	0
Hernia (um- bilical and ventral) ....	4	26	Vomiting, 1 Infection, 1	0	2	0	0	0	0	2 (cholemia).
Stricture of rectum.....	1	29	.....	0	0	1	0	0	0	0
Carcinoma of uterus.....	1	27	.....	0	1	0	0	0	0	0
Floating kid- ney.....	1	28	.....	0	0	1	0	0	0	0



evidence most emphatically favors the early removal of gall-stones. The mortality will be very small, the proportion of cures very large, and the hazard of a return of the patient to the hospital for a second operation very slight. In the light of the results secured in this larger series of cases we believe that our stand of a decade ago, which favors the removal of gall-stones associated with other gynecological or abdominal lesions, whether they are producing symptoms or not, is amply sustained.

In the accompanying summaries of case histories (Tables I, II and III) all patients have been accurately traced, and the final results, as tabulated, were obtained within two months of the preparation of this paper.

TABLE II.—COMBINED OPERATIONS WITHOUT GALL-BLADDER SYMPTOMS.  
By FRANK B. BLOCK, M.D.

	No. of patients.	Days in hospital.	Convalescence.	Returned for second operation.	Cures.	Great improvement.	Slight improvement.	Unimproved.	Worse.	Death.
Fibriod.....	14	80	Vomiting, 2 Phlebitis, 1 Infection, 2	0	8	4	0	0	0	0
Displacement.	5	25	.....	0	1	0	0	0	2	0
Ovarian cyst.	5	33	Cystitis, 1	0	3	0	0	0	0	1; two years later; cause unknown.
Pelvic inflam- mation.....	3	25	Infection, 1	0	1	1	0	0	0	0
Displacement and hernia.	2	24	.....	0	2	0	0	0	0	0
Appendix.....	1	18	.....	0	0	0	1	0	0	0
Cervical polyp	1	48	.....	0	0	0	0	0	0	1; cerebral hemorrhage six yrs. later.

TABLE III.—COMPARATIVE STATEMENT OF SIMPLE AND COMBINED GALL-BLADDER OPERATIONS.

By FRANK B. BLOCK, M.D.

	Simple gall-bladder operations.	Combined operations with gall-bladder symptoms.	Combined operations without gall-bladder symptoms.	Total.
Number of cases.	55	73	31	159
Percentage of cases traced...	84.0 per cent.	78.0 per cent.	86.0 per cent.	86.0 per cent.
Average age of patients.....	42 years.	39 years.	44 years.	41.7 years.
Average number of days in hospital.....	29.4	28.6	29	29
Complications of convalescence:				
Infection....	5.9 per cent.	9.0 per cent.	9.7 per cent.	8.2 per cent.
Prolonged vomiting..	.0	4.0 per cent.	6.4 per cent.	3.1 per cent.
Phlebitis....	2.0 per cent.	2.6 per cent.	3.2 per cent.	2.5 per cent.
Pneumonia..	.0	1.3 per cent.	.0	.6 per cent.
Returned for second operation.	.0	9.5 per cent.	.0	4.4 per cent.
Postoperative history:				
Cured.....	69.5 per cent.	59.7 per cent.	64.0 per cent.	63.8 per cent.
Great improvement.	15.2 per cent.	17.5 per cent.	16.0 per cent.	16.1 per cent.
Slight improvement.	.0	1.7 per cent.	4.0 per cent.	1.5 per cent.
Unimproved.	2.1 per cent.	8.7 per cent.	.0	4.6 per cent.
Worse.....	.0	.0	8.0 per cent.	1.5 per cent.
Died:				
In hospital..	4.3 per cent.	7.0 per cent.	.0	4.6 per cent.
Outside hospital, incident to operation....	.0	1.7 per cent.	.0	.7 per cent.
Independent of operation subsequent to discharge from hospital.....	8.6 per cent.	3.5 per cent.	8.0 per cent.	6.1 per cent.

NURSING.

HOSPITAL SOCIAL SERVICE.<sup>1</sup>

By MARGARET S. BROGDEN,

*In charge of the Social Service Department of The Johns Hopkins Hospital.*

There is no branch of the nursing profession that is attracting such general interest to-day as public health nursing, and surely there is none that gives more satisfactory returns for our labor. The increasing demand for the socially trained nurse demonstrates the place preventive medicine has taken, not only in the minds of physicians, but also of heads of municipal departments, business firms, and the thinking public, and the effort that is being made to eradicate causes by attacking bad social conditions rather than treating the symptoms of these abuses.

All forms of public health work are so closely related, and so

<sup>1</sup>Read at the Twenty-fifth Anniversary Celebration of The Johns Hopkins Hospital, October 5, 1914.

interdependent, that while each agency has its special function, we must work in cooperation, as different parts of a great machine, to obtain the desired results and at the same time prevent duplication and overlapping.

The hospital social service is the center toward which all branches lead. The district nurse brings her patient to the dispensary for diagnosis and treatment; the child-placing agent must have her little charge examined before placing her in a foster home; no fresh-air institution will receive a guest without a doctor's certificate; the perplexed Federated Charities worker turns to the dispensary to learn if the man who will not support his family is ill or lazy. The social service acts as the exchange between the hospital and the outside agencies,



while we, in turn, depend upon these outside agencies to assist in carrying out the plans made within the hospital to hasten and safeguard the recovery of our patients.

Social service in hospitals, in one form or another, has existed since a very early period, being practised by kindly disposed individuals, usually of religious orders, and by the doctors and the nurses.

Miss Richards tells of reading in the report of a dispensary as early as 1806 of the doctors and the directors of the dispensary providing patients with surgical appliances which they could not afford to purchase for themselves. And again we read that in 1860, Dr. Blackwell, influenced by Florence Nightingale, her personal friend, had the families of patients at the New York Infirmary for Women and Children visited, instructed in hygiene, and provided with food and clothing when necessary.

In 1905, the first organized social service was established by Dr. Richard C. Cabot, who placed a nurse in the out-patient department of the Massachusetts General Hospital as a definite factor in dispensary treatment. So convincingly did she demonstrate her usefulness that from this small beginning has developed the present widespread interest; and though I think there has been no census taken, and I cannot give the number of such departments in hospitals and dispensaries, they are very numerous, and few large hospitals consider their organization complete without a social service department.

Dr. Cabot tells us that he got his idea of social service from the work Dr. Charles P. Emerson was doing with the medical students at The Johns Hopkins Hospital. Dr. Emerson's student board was organized in 1903, two years prior to the organization of social service at the Massachusetts General Hospital.

The Johns Hopkins Hospital Social Service Department was established in 1907. A lay worker from the Federated Charities had charge. After eight months she resigned on account of ill health, and the department was closed for four months. In August, 1908, it was again opened, with Miss Wilmer, now Mrs. Athey, in charge. She reorganized the work, and under her able management, it became a permanent and valued part of the hospital equipment.

We are most fortunate in our form of organization, being an integral part of the hospital and receiving support and cooperation from the management, such as is enjoyed by few or no other social service departments.

Our work is philanthropic only in so far as all hospital or other work that is for the good of mankind must be regarded as philanthropy; but we are in no sense a relief-giving agency and should not attempt to carry on work when we can refer it to others better equipped to handle the special problem. Medical social service concerns the health of the individual only, while the Federated Charities deal with his social status generally, each being dependent upon the cooperation of the other in perfecting a plan when both sickness and poverty are present.

A child may need glasses, and the family be too poor to purchase them. We must see that the glasses are provided and

that the child returns to have them tested and properly adjusted; but it is the duty of the Federated Charities to discover and remove the cause of the poverty.

Our object, then, is primarily to increase the efficiency and raise the standard of hospital and dispensary treatment. We endeavor:

(1) To bring to the physician's knowledge those contributing factors to disease furnished by the social and economic conditions under which the patient lives.

These can only be determined by home-visiting and a closer personal relationship than can be established in the limited time allowed by the visit to the crowded dispensary.

(2) To make it possible for the patient to carry out the doctor's instructions by judicious use of his own resources or by connecting him up with the proper agency.

That we are to some extent doing this I think I may justly claim. The following example will illustrate:

Two children, age eight and ten, were under treatment in the children's clinic. Diet, regular hours of sleep, including an afternoon nap, had been prescribed, but as the children showed no improvement, they were referred to the social service department for home investigation.

We learned that the father had come from Russia several years ago. He had sent all his earnings back to Russia to bring his family to this country. After they had arrived the wife and one child were found to have trachoma and were not allowed to land. His two other children who came to Baltimore were placed with a Jewish family who occupied two rooms in a crowded tenement. As there were not beds enough for the children of the family, the little visitors slept on the kitchen floor. The father was once more saving his earnings to pay his wife's passage again to this country.

We were able, through cooperation with the Hebrew Benevolent Society, to have the children moved into two rooms with their father; and a proper person was placed in charge, who taught them to prepare their food and saw that the doctor's instructions were carried out.

During the last eighteen months our work has greatly extended. Eighteen months ago there were two workers and one secretary. Our present staff consists of a social worker-in-chief, who has general supervision of the whole department, nine assistants, and two secretaries. Two additional assistants are being arranged for.

To each worker is assigned a certain group of patients. The hospital wards are visited by Miss Adamson, who makes daily rounds after having received the list of admissions of the previous day. She talks with the new patients, who readily tell her, it may be, of children left at home without proper care, of the anxiety of the family, who did not know the patient was coming to the hospital, or whatever trouble is paramount. Numbers of patients coming from a distance have never traveled until coming into the hospital and do not know how to buy their return tickets, or, in some instances, by what railroad they may reach home; while others, when discharged from the hospital, have no places to which they may return



until sufficiently recovered to earn money with which to pay their board.

The time came, for example, for the discharge of a patient on Ward G. She knew the name of the little town in which she lived but did not know the state. We found that there was a town of that name in each of the states of North Carolina and Ohio, and it was not until we learned her doctor's name and looked up his address in the medical directory that we were able to tell in which state she belonged.

Miss Adamson tells me that a convalescent home is the greatest need she finds in her ward work.

A striking example of the necessity for a social worker in the wards is the following:

An old lady, showing senile changes, was brought to The Johns Hopkins Hospital by a policeman who had found her at Union Station, where she had spent the night. She was admitted to Ward G. When ready for discharge her relatives could not be located; she had no money, but when asked her plans, she said she was going to the Belvedere Hotel and gave the office of a well-known lawyer as her home address. He was visited, but refused to give assistance in the search for her friends. Later, we succeeded in getting from her the address of a lodging-house where she had stayed. On visiting the landlady, we learned that she was the widow of a U. S. army officer. She receives a quarterly pension of \$60 from the United States Government. This she spends as soon as she receives it and then wanders around, sleeping in public places or wherever she can find shelter. The landlady had kept her for some time, but as she paid no rent and had to be provided with food, she was obliged to turn her out. She has no immediate family, but we finally learned the name of a relative, who was visited and assumed the responsibility of placing her in a private asylum.

In the dispensary there are in the departments of:

Medicine .....	1 worker
Neurology .....	1 worker
Ophthalmology .....	1 worker
Phipps Tuberculosis Dispensary.....	1 worker
Orthopedic Dispensary.....	1 worker arranged for
Harriet Lane Home for Invalid Children.	1 worker
Henry Phipps Psychiatric Clinic.....	2 workers

In August, 1913, it was decided to place out in families the children from The Johns Hopkins Colored Orphan Asylum. The selection of suitable homes and the supervision of the children were put under the direction of the social service department, and a social worker was appointed who has carried on the work very satisfactorily.

The workers are in the clinics during dispensary hours. This not only brings them into active cooperation with the doctors in the clinics, but enables them to see practically all of the patients, and to establish friendly relations with them, and often to make the social diagnosis that has been overlooked by the busy physician.

Upon the recommendation of Miss Vincent, the social worker in the medical clinic, tooth brushes and powder are being dispensed from the pharmacy on the same basis as the medicines. Dental treatment is secured for patients through the dental

departments of other hospitals. Arrangements are, however, now being made to have a dental clinic at The Johns Hopkins Dispensary.

We have been able to secure the services of a woman, who comes to the dispensary once a week to take orders for abdominal bandages and to fit them to the patients, the doctors approving them before delivery.

Through cooperation with the Young Women's Christian Association, we have secured pupils from the domestic science class to visit the homes of patients from the gastro-intestinal clinic and instruct them in the selection and preparation of food.

We have established a filing system by which the doctors indicate the date for the patient to return. If he fails to report on that date, he is written to; and if this does not bring him, the doctor is consulted, and if necessary the worker visits the home, and urges him to return.

It was found that many patients for whom glasses were ordered, were having them made by unreliable opticians, and others were too poor to purchase them.

We were asked to consider the best means of securing good glasses for the patients. An arrangement was made with a firm of reliable opticians by which all orders are filled by it. It sends an agent to the dispensary daily, who fits the new glasses and takes orders for others. All patients are seen by the social worker, and those unable to pay for glasses are allowed to make small weekly or monthly payments. This same method is used in securing braces and other appliances.

Persons who cannot be admitted to The Johns Hopkins Hospital are sent to the social service department to make arrangements for admission to other hospitals.

By taking the census of the dispensary we learned that the attendance in the neurological clinic in June and July, 1913, before a social worker was installed, was: new patients, 146; old patients, 840; and the attendance for the same months in 1914, since the social worker has been installed, has been: new patients, 163; old patients, 914, showing a percentage of increase of 11.6 for the new and of 8.8 for the old.

Using the same method for the department of ophthalmology, we find the percentage of increase for the new is 7.2 and for the old 7.5, since a social worker has been working in connection with the clinic.

At the same time, four patients only for whom glasses were ordered did not get them, and that owing to the fact that they refused to follow the doctor's advice.

A study of feeble-minded children is being made in The Henry Phipps Psychiatric Clinic, the social workers cooperating with the juvenile court and the schools, from which many wayward and backward children are sent to the clinic for mental examination. Many of these children show a mental retardation that places them far below their actual age. They are taken from the regular classes and put into ungraded or special classes, or entered in institutions for the feeble-minded, the social service acting as intermediary between the physician and the court or the school.

The Maryland Bureau of Statistics and Information avails itself of the opportunity of sending the children who apply



for a work-permit for examination; the social worker returning to them the certificate signed by the physician.

In The Harriet Lane Home for Invalid Children, the social worker is at the admitting desk. In this way she establishes the desired relationship with the patient, and by questioning the mother she can judge how well she has understood the doctor's directions and whether she has facilities for carrying them out, and when necessary can refer them to the district nurse or relief agency.

We try to limit our work to the clinics to which the workers are assigned, but are forced at times to depart from our rule, as in the following case:

One of the surgeons came to the social service department saying: "I know you do not take cases from the surgical clinic, but you must see M., who has attempted suicide, and if I send him away without a friend, he will surely try it again."

M. was a young German, about 19 years old, of fair education and pleasing appearance who had been in this country a few months. Owing to his lack of English, and of knowing to whom to apply, he had been unable to secure work. His only relative in this country had refused help. Both money and courage gone, he shot himself.

Two of the medical students, who spoke German, offered to take charge of him until we could make a plan. We visited the North German Lloyd Steamship Company and told the story to the agent, Mr. Henry G. Hilken, who offered to send him back to his friends in Germany free of charge. Later, we had a post card from him telling of his safe arrival at his sister's home in Germany and thanking us for the interest we had taken.

A volunteer committee, composed of the married nurses living in Baltimore, the wives and the daughters of doctors and trustees, and others interested in our work, has been of great assistance to us, not only by giving generously of their time and interest, but by raising money to pay the salary of one worker and also an emergency fund to be used for the benefit of patients. Without our volunteer committee, much of the work we are now doing could not be undertaken.

A number of them have learned basketry and other occupational work, to enable them to meet with and instruct the patients during dispensary hours. This is not only of therapeutic value, but lessens the tedium of waiting their turn to see the doctors. The baskets are sold, the proceeds over the actual cost of the materials going to the patients.

Another group to whom we are much indebted for their ready cooperation is the medical students, many of whom work under our direction and have given very valuable service.

There is one point that I always try to emphasize when speaking to a group of nurses, and that is our unpreparedness for medical social service and our need of special training to fit us for this work. The training schools give us all that is possible, but already the courses have become so full that it is hard to crowd them into three years, and they cannot give the thorough knowledge of social and economic conditions that we must have. I am going to quote from an editorial in the *Public Health Nurse's Quarterly* of two years ago that applies to-day as well:

When a graduate nurse first enters the field of district nursing, she does not, perhaps, quite realize what a very different kind of work she is taking up from any she has heretofore undertaken.

The bedside care is the same, the reports turned in to the physicians will be made out in the same way, perhaps even the observation of the patient may be more or less the same—I say "more or less," for the social condition of the patient will now enter largely into the treatment of his physical condition, and for that reason must be specially observed. But with these three features of a district nurse's work, *i. e.*, the bedside care, the medical record, and the general observation of the patient, ends practically all resemblance to her former work. Hitherto she has been an observer of medical problems only; she now deals with social problems as well.

If this be true of district nursing, where the bedside care plays so large a part, it is doubly true of hospital social service.

Up to the present time we have no students from the training school, but we are aiming, as soon as the school has grown large enough to care for the numbers of patients the new buildings will bring into the hospital, to have an elective course of four months by which three of the senior nurses may have training in the social service department.

We are at present giving a four-months course to post-graduates in affiliation with the Federated Charities; two months field-work being given with the Federated Charities and two months with the social service department. This is only open to graduate nurses and to workers who have already had social training.

We feel that this is not adequate training, but it is helpful in that it gives nurses some knowledge of social conditions, and the social workers a better point of view of the medical work. It is valuable to us in bringing about cooperation between the hospital and outside agencies as well.

## THE VISITING NURSES OF BALTIMORE.<sup>1</sup>

By MARY E. LENT,

*In charge of The Instructive Visiting Nurse Association of Baltimore.*

In the field of visiting nursing the Johns Hopkins nurses have taken active part. Twenty years ago public-health work, as we now call it, was in its infancy—in the pioneer stages—an experiment whose development no one could foresee. To

<sup>1</sup>Read at the Twenty-fifth Anniversary Celebration of The Johns Hopkins Hospital, October 5, 1914.

give nursing service to the sick poor of a community was an undertaking for which there was doubtless need; but how great the need, how valuable the preventive work, how wide-spreading the results of this education, time alone has been able to prove.

The first nurse to do district nursing in Baltimore was Miss



Evelyn Pope, now Mrs. J. Williams Lord, who went on duty in January, 1896, nearly nineteen years ago, and worked alone for six months. In July, while on a vacation, she was relieved by Miss Anna C. Jack, now Mrs. Frank Smith. But Mrs. Smith did not give up the work when Mrs. Lord returned from her vacation; they both worked together in this untried field of social service, Mrs. Smith for a year, Mrs. Lord for two years and three months. The work of these two nurses was the nucleus from which has arisen The Instructive Visiting Nurse Association of Baltimore.

The first head nurse of the newly formed association was Miss Ada M. Carr. For six years she was in charge of the new work, and conducted it safely through the struggling pioneer stages and proved its worth to the community. It is due entirely to Miss Carr's tireless energy, ability and foresight that the new undertaking was successful, and it was she who laid the broad foundation of the work as it exists to-day. In September, 1903, Miss Carr resigned as head nurse of the association, and Miss Mary E. Lent, one of the nurses who had been on the staff for two or three years, was appointed to fill her place. Since that date, 1903, to the present day, Miss Lent has been in charge of the association. Be it noted in passing that the establishment of the Visiting Nurse Association of Baltimore was contemporaneous with that of similar work founded at the same time in other cities, in New York, Boston and elsewhere, Baltimore being one of the first half dozen cities to undertake this pioneer work.

The reports of those early days are interesting. In 1897, at the end of the first year's work, we find that the two nurses of the association had paid over 3000 visits to the patients under their charge. During 1898, we find the staff of nurses increased to four, with a total of nearly 5000 visits. In this year the work of the Thomas Wilson Sanitarium was also placed in charge of the Visiting Nurse Association, upon whom devolved the task of selecting and sending out babies to the sanitarium. This special branch of the work was carried on for several years, until the work developed to such an extent that a separate association and a separate nursing staff were demanded to care for it. This new work, now called the Infant Mortality and Babies' Milk Fund Association, was placed in charge of another Johns Hopkins nurse, Miss M. Grace O'Bryan. She was succeeded by Miss Gertrude Miller, who was in charge of the work for three years.

In 1900, we find the work of the Visiting Nurse Association steadily increasing, as indeed it has always done since its foundation. In that year its five nurses visited over 1500 new patients, and paid something over 10,000 visits. In 1903 the association was given as a home, or headquarters, the house at 1123 Madison Avenue, donated by Mrs. Bertha Rayner Frank. Up till that time the nurses had lived in their own homes in different parts of the city, but when the Rayner home was given, the working staff took up its residence there.

The first school nurse in Baltimore was one of our nurses, Miss Florence Hunt, who was on the staff of the association until she received her appointment as school nurse. It is interesting to notice that the pioneers in public-health work in Baltimore are Hopkins graduates.

Ever since its origin, the nurses of the association have cared for tuberculous patients. Such cases were given nursing care on exactly the same terms as those of typhoid fever and other medical cases, and the visiting list has always included a number of consumptive patients. In January, 1903, however, a special tuberculosis nurse was placed on duty, whose entire time was devoted to cases of this character. This first nurse was Miss Nora Holman, of our school. Miss Holman did this special work for three months, and the next Hopkins nurse to undertake it was Miss Ellen N. La Motte, who came on the staff of the association in June, 1905. From 1903 until 1910—a period of seven years—the Visiting Nurse Association had a special staff of tuberculosis nurses as well as a staff of general nurses. Upon January 1, 1910, the special tuberculosis work of the association was transferred to the Baltimore Health Department, with Miss La Motte in charge of the work.

Thus we see that the Visiting Nurse Association has been the parent trunk from which branches have sprung and been transplanted elsewhere—the infant-welfare work, the school work, and the tuberculosis work of the city all at one time having been done in connection with the association, and by nurses graduated from The Johns Hopkins Hospital. But as each branch has developed and been transplanted elsewhere, the main trunk of the association has continued to grow with ever increasing vigor. The report of 1913 shows fifteen staff nurses, who during the year visited 8500 patients, paying them a total of 55,000 visits. It is difficult to conceive what this means to the community; it is not the actual nursing, valuable as that is, but the preventive work and the educational value of these visits which count.

An interesting new phase of our work was the special eye work, begun by Miss Christina Dick in June, 1912, and continued by Miss Katherine Olmsted, both nurses of our school. This work consisted in caring for and putting under treatment eye cases only. The preventive value of this special work is hard to estimate. For example, the nurse was called to a girl of sixteen, who had been working as a cigarette roller, thereby helping to support the family. One day she complained of pain in her eyes, and on the next was unable to open them at all. For six weeks she sat about the house, suffering intense pain, and unable to open her eyes except spasmodically. When discovered she was in a pitiable condition, and so thin and weak that it was several days before she could be fed up sufficiently to go to the dispensary. There a diagnosis was made of congenital syphilitic keratitis, and salvarsan was later administered. Four days later, the eyes which had been closed for weeks, opened, and later the lesions disappeared with astonishing rapidity, and the girl was able to resume her employment. This eye work, however, valuable as it would seem to be and greatly as the community needs it—one nurse cared for 637 patients within a period of six months—was not supported by the public and for lack of funds was discontinued. The association, however, has successfully demonstrated the need for such special service.

The activities of the association are spreading out into the counties surrounding the city of Baltimore, and public-health



work has been done at Ellicott City, Catonsville, Highlandtown, Brooklyn, Mt. Winans, and other villages. The object of thus extending the work beyond the city limits is partly to train the nurses, so that they may understand how to conduct work in a country community, under certain handicaps not met with in city organization; also to prove to these various communities the need and value of public-health work. As the communities realize this need, they establish and finance their own nurse.

The larger towns in Maryland, such as Frederick, Annapolis, Hagerstown, Rockville and Cumberland, also look to the Visiting Nurse Association for their trained workers. Members of

the staff have also been sent to other states than Maryland to start public-health work of various kinds.

All the facts go to prove that the training given by work under the Visiting Nurse Association furnishes an invaluable equipment for special public-health work such as tuberculosis nursing, infant welfare, school and industrial work, hospital social service, and the like.

This is but a brief and inadequate summary of the activities of our nurses who are doing social work in connection with this association which was established so many years ago. Its foundation, development and extension have been due to the initiative of the graduates of this school.

## NURSING IN THE HENRY PHIPPS PSYCHIATRIC CLINIC.<sup>1</sup>

By EFFIE J. TAYLOR,

*In charge of the Nursing Department of The Henry Phipps Psychiatric Clinic.*

The gift of The Henry Phipps Psychiatric Clinic to The Johns Hopkins Hospital and Medical School has given to the medical student an opportunity, unprecedented in this country, to study mental disease at close range; and likewise an opportunity to the student nurse in The Johns Hopkins Training School to study the nursing care of mental patients.

The experience of those who knew most about mental work, was that in few cases was it possible to get in touch with patients suffering from such disturbances till conditions were so serious that the patient could not be endured in the household; consequently, to obtain relief for the family from the discomfort, a physician was consulted—in many cases simply a general practitioner, who knew little or nothing about mental illness—and in order that the condition might not become known, the patient was hurried away to a hospital or retreat, without much consideration as to whether or not the place or its environment was what that particular case needed.

The condition described, with the results obtained, was largely responsible for a feeling of hopelessness even among scientific medical men, which was to a greater extent shared by the laity. A mental illness was felt to be something absolutely different from any other type of illness, something to which a stigma was attached, to be secreted and never discussed. The great problem presenting itself to physicians trying to cope with such conditions was, how to come in touch with mental illness at its onset, and how to prevent its development.

The inability of the general practitioner to recognize an early abnormal mental condition was apparent, perhaps due entirely to a lack of opportunity for study. The course in psychiatry—in most medical schools—included simply a small group of lectures with perhaps a clinic or two in a state hospital or in the insane department of a city hospital. In these institutions one rarely sees an incipient case. With statistics showing the great increase in mental disease, and no adequate means to cope with it, the need of a hospital connected with a medical school, affording opportunities to the student for study, with the advantages of well equipped laboratories for research

and teaching work, prompted the gift by Mr. Phipps through Dr. Welch to The Johns Hopkins Hospital and Medical School.

Here, because a part of a general hospital, it is possible to induce patients, describing themselves as "only a little nervous," to come to the clinic dispensary or consulting rooms, where mental physicians and diagnosticians are equipped to study each case and advise as to its care. If deemed sufficiently ill, admission to the hospital is encouraged, and while a patient is never deceived regarding his illness, great care is taken to make him feel that it is a *hospital* to which he has come, and not a hiding-place or place of imprisonment.

The medical students are assigned to work in the mental dispensary for a certain period, in the same way that they are assigned to work in the medical and surgical dispensary in a general hospital.

It is in this, and in the fact also that opportunity is given the pupil nurses in their regular course to establish firmly in their minds that physical and mental illnesses must be studied together, and are each an equally important part of their professional education, that the hope of the future rests. With a sound knowledge of existing conditions, and a hopefulness born of that knowledge, they will be able to meet and appreciate early symptoms, and give encouragement to those needing treatment. When they are able to teach because they will know that mental disorders and peculiar behavior are the result of mental illness, the same as physical disorders and abnormalities are the result of physical illness, the hopeful day for mental nursing work will have arrived. And such is the mission of the clinic. It is essentially educational in its purpose.

A great many questions have been asked regarding the type of patients admitted to The Henry Phipps Psychiatric Clinic, and perhaps it may be interesting to some of you, at least, who are not familiar with the plan of the building, to tell you something of it, and why certain cases can be satisfactorily taken care of here, and why others cannot.

The situation of the building in the midst of a general hospital and facing the street on two sides indicates at once the difficulty of caring for patients disturbed and noisy over a prolonged period. This on the outset is a severe handicap, as often

<sup>1</sup>Read at the Twenty-fifth Anniversary Celebration of The Johns Hopkins Hospital, October 5, 1914.



the most encouraging results would be obtained, could we tide over that period of exhilaration, but the fact that the windows must be kept closed, and the patient kept within doors, makes the clinic far from ideal for accomplishing the desired result if a long time has to be covered. At the same time disturbed and excited patients are not refused admission to the clinic, and a large number of cases, even under this apparent handicap, have been cared for and successfully guided over this difficult period of excitement, which was unquestionably shortened by the individual nursing care and attention which it has been possible for us to give.

There is another group of patients, also, which after a time generally requires to be transferred to other hospitals, where there are greater outdoor facilities. This group is composed of patients who have a long, slow convalescence—patients who tire of indoor amusements and occupations and who need more strenuous physical exercise. Such patients, after they have gained an insight into their own condition, when they have arrived at the place where they can appreciate the cause of their illness and are willing to accept it and make a fight to overcome it, many times make a more rapid recovery if sent to a hospital in the country where they may live an out-of-door life.

Another group of patients, which cannot with the best results be treated in this clinic, is that which fails to cooperate in treatment, whose recovery is slow or retarded, and in which nature may reassert herself, or otherwise, without the assistance of the individual. This group and that one in which mental deterioration has become so marked that little can be hoped for by educational means, are usually transferred to an institution where greater provision is made for the care of patients of these types.

Patients are not, however, classed as chronic and acute and only acute cases kept, as is sometimes the idea abroad. Any case willing to cooperate in the treatment, or when the family is willing to do so, may be admitted, unless there is some unusual reason to do otherwise.

It is not the case either that patients can only be retained for a short time. Some of our patients have been here for five, six, and even twelve months.

The plan followed in assigning the patients to the various wards in the hospital is:

To separate the disturbed and agitated from the quiet; those acutely ill from those less markedly so; those willing to cooperate in every way from those more resistive, or antagonistic. Each individual case is considered, according to the special needs of the patient, based upon his peculiar characteristics, and his environment is chosen according to his condition and not according to the diagnosis of the disease.

The most acutely ill patients are admitted to the first floor, and as improvement progresses they are transferred to the second and then to the third, or convalescent ward. You may be interested to know that during many hours in the day some of the patients on the first floor are in a condition to mingle in class, or in recreation, with those on the two upper floors, and it is thus a great stimulation to them to strive to go up higher.

The clinic was opened for patients on May 1, 1913, when one patient was admitted.

We felt very rich that night, for we had in the hospital eight head nurses, with only one ward open and one lone patient; but our grandiose ideas were short-lived, the next night a feeling almost of despair possessed us. New patients were admitted all day, and one ward after another was opened; by night we had nine patients on four different wards—the private male and female wards and one male and one female public ward.

And this at once engulfed our eight head nurses, four on day and four on night duty, with no pupils to assist. Nine patients may not count for much, but let me remind you that there are patients and patients. Not since that day have we admitted eight such ill patients in a week—and this was in *one day*.

Then, to add to our distress, the workmen were everywhere in the building. The windows would not stay open, necessitating the change of every pane of glass. The continuous-bath tubs would not work. The gas stoves leaked and could not be used. The refrigerating plant was not doing its duty, and we had no drinking water.

One of the patients was so destructive that almost every time rounds were made some new disfigurement of his rooms was reported, and over this we were indeed sad.

We continued admitting, and by June 1 had forty patients.

The question of how we were to care for our patients, who had come in more rapidly than we had the least expectation of, before the building was finished, and before the training school was in a position to supply the nurses, presented itself with great urgency. It was impossible to obtain a large enough number of graduate nurses who had had any experience to fill the positions, and those who had not, who came on trial, were so timid many of them would not remain.

It seemed necessary, therefore, for the sake of our patients, to employ a limited number of attendants who had had some previous experience to assist in the wards till our nurses could be given a proper training. I am quite convinced that such attendants have a very definite and useful place in such a hospital as this. We were fortunate to find several refined, dignified and intelligent women who gave valuable service.

It has been necessary, obviously, to define and limit their duties and responsibilities. They do not live in the hospital, but have their meals here in a dining room provided especially for them. They do not wear caps, and they understand their position is simply that of a helper, and their work absolutely under the direction of the nurses on the wards. And up to the present we have found no disposition on their part to overstep their privileges. Whether or not it would be desirable to furnish a special uniform and give a certain amount of training, making them a permanent group in the hospital, is a question open for discussion. There is no doubt in my mind that a great deal of valuable time may be saved for the nurse, and a great deal of the work necessarily burdensome and irksome in connection with ward duty may be spared the senior nurse, and be taken care of quite as well by the attendant, leaving the nurse free to spend her time altogether with and for the patient; and as mental patients are the most trying and difficult type to deal with, the nurse who cares for them needs all the physical help and support she can get. Then, too, our nurses are on duty



in this clinic for only a short time, and it is desirable that their time should be spent in the way that will be the most helpful to them, and which will be of the greatest educational value.

Our day staff consists at present of:

Assistants .....	2
Graduate head nurses.....	10
Postgraduates .....	6
Graduates—ward duty.....	2
Social-service workers .....	2
Pupils .....	5
Occupation teachers .....	2
Women attendants .....	6
Physical instructors .....	2
Orderlies .....	8

Night staff:

Night superintendent .....	1
Graduates in charge of wards.....	5
Postgraduate .....	1
Women attendants .....	6
Orderlies .....	6

The course for pupil nurses was opened in October, 1913, with six pupil nurses on duty. Since that time 53 pupils, senior and intermediate, have had experience in this department.

The plan is to allow a period of two months for each pupil during her intermediate or senior year. At the close of her three-years course an opportunity is given to any nurse desirous of completing the six months necessary for a special certificate, to take the additional four months. The schedule for the eight weeks practical instruction is arranged to give experience in private, convalescent and disturbed wards, and in the hydriatic, gymnastic and occupation departments.

The instruction in the hydriatic and gymnastic departments includes treatments by electricity, various water baths, salt rubs, massage and physical exercises.

Instruction in the occupation department is given in weaving baskets, sewing, embroidery, and other forms of fancy work, together with the diversional occupations.

Two instructors are provided, both nurses, with special training in the hydriatic and gymnastic departments, and two in the occupation department, the latter two not being nurses. The pupils are admitted to the classes, not as helpers merely, but specifically for instruction, and are required to do a certain amount of work.

The theoretical work, given last year to the pupils in training, included:

Lectures on mental disorders.....	8
Tests and treatments in mental disorders, with laboratory demonstrations .....	4
Lectures on mental hygiene.....	3
Classes and demonstrations.....	9

24

You will ask, perhaps, what is our pupil nurses' attitude to this branch of nursing. With few exceptions we find the nurses enthusiastic about the work. As is always the case, however, some enjoy it more than others, and all are not equally fitted for it.

It is always interesting to get as many points of view as possible on any subject, but it has been especially so in this work. There are some who feel that any kind of person, pro-

vided she has a strong physique, will do for mental work. Strength of body is the pre-requisite—strength of mind and culture a secondary consideration. We have heard such expressions as this: "I do not see what value the training can be to pupil nurses. They only get into bad and irregular habits, because you have no routine."

With reference to the first opinion, while of course health and strength of body are pre-requisites to any branch of nursing, for obviously there is a heavy physical strain connected with it, in no branch of nursing is the cultured, versatile, adaptable and highly trained mind more needed than in mental work. In most instances physical fitness is secondary to mental fitness, and you need hardly ask me why.

To begin with, the illness is an illness of the mind—an inability on the part of the patient to adjust his behavior to his environment. And what does that mean? Anything of which you have imagination enough to conceive. A man whose mental control has been inhibited by lack of a proper inheritance, disease, bad habits of thought or of the emotions, or whatever the cause, may be silent, depressed, apprehensive, or excited, exhilarated, emotional. He may be stupid and demented, or brilliant and imaginative; may be apathetic and unresponsive, or vivacious and animated; may be crafty and secretive, or open and talkative. He may be neat, clean and scrupulous, or untidy and careless in his habits; he may be belittling in his ideas of himself, or he may be pompous and important. It is impossible to tell what you may find.

And what is the nurse's task?

First and foremost, to correct her view-point. It is seldom that a nurse comes to us with the full realization that our patients are ill. That is her first lesson; once having learned it all else is plain. Second, that there is nothing sensational or sentimental in the care of our patients.

The question we are frequently asked by the student nurses is, "What can we read on the subject of abnormal psychology?" Or, "I have read an article on dreams. Please tell me what such and such a dream means." We say we do not know; that is not our problem. Sensational psychological literature has no place in a nurse's library. There are only a few text-books on abnormal psychology or psychiatry that the professors in our clinic are willing to recommend for our nurses' reading, and why? Simply for the reason that the study has not yet an authoritative background, and with only the limited knowledge of the subject it is possible to give the nurse in so short a course, she is not prepared to discriminate and sort out the contradictory statements and apparent disagreements and glean the truth, if truth there is. It is our experience that for the most part there is so much that is sordid, emotional and sensational in much of the literature, so much that is experimental, uncertain and contradictory, that one should choose with care, for even those best informed on the subject become confused with the variety of ideas expressed on any specific condition. But we have some firm ground to stand upon, and it relates more to the field of nursing than, perhaps, to the field of medicine. We are assured, by our own observations and those of physicians here and elsewhere, that nursing in mental cases is a thing that counts.



We also have an opportunity to make observations with reference to the kind of nurse whose efforts count for most, for we have attendants with only practical experience, nurses with somewhat limited advantages and our own pupils and graduate members of our staff who have had general and special training for this work. It is most gratifying to tell you that our own nurses (with few exceptions), even with the limited experience we are able to give them, do a work that counts; and without exception our physicians, whether from The Johns Hopkins, or from state hospitals or from afar, voice the same opinion.

The conclusion obviously to be drawn is that the woman is the important thing—one fitted by her natural inheritance and by her education—and the woman who is the most successful in this work is the one who has complete possession of herself; one who understands and appreciates human nature; one who has a keen sense of her relationship to others, who has judgment, patience, observation and tact; who knows the great advantage of silence, but at the same time knows when to speak; the woman who has had the broadest culture acquired by reading or travel, who has added to her general education many accomplishments, thus making her interesting, versatile and resourceful—such a woman we crave for our mentally ill patients. When more of the type above described are in our mental hospitals (and for that matter in our general hospitals as well), we may look for astounding results, even though the doctors are still debating over whether or not in dementia præcox there is a pathological change in the brain cell, or whether psycho-analysis is the proper method of treatment to employ in functional neuroses. The nurse, properly equipped herself, who cooperates with the physician and enters into the life of her patient, can do more than any one else to establish proper habits of thought. It is she who spends hours with the depressed patient, or the one whose mind is filled with the sordid things of life. If she can substitute from her own experience something else to take the place; if she has patience to plod on and courage to believe, as Dr. Osler says, that life is a habit—a succession of actions that become more or less automatic—that one trial after another, one failure after another gives power, she will not become discouraged, though the process seems slow, but eventually will accomplish wonderful things. And not alone does the ideal nurse need physical and mental power, but she needs moral and spiritual power as well, for there is no kind of work, no association with humanity that brings one more in contact with the grosser side of life than does mental work. Thus it is she needs the uplifting support which comes alone through contact with the moral and spiritual influences.

There is still that other question asked previously: "How can work in a mental hospital be good training for pupil nurses, in that here you have no routine?"

To be sure, we have not the routine of a big, busy, bustling public ward filled with medical students, but we have a routine, nevertheless, and one which seems to me more conducive to the development of good nursing. Most principals of training schools deplore the fact that they are handicapped by routine in their teaching in a large general hospital.

It is true, however, that in the type of patient with whom we have to deal, we have to avoid, more or less, certain fixed methods of work. For the most part, with us, it is more important that a certain result be obtained, rather than that a specific method be observed. At the same time we try to adopt all the general nursing principles taught in the general hospital, and employ them whenever possible. The nurses are told on entering that the general nursing procedures taught previously are all to be observed in this department in so far as they are applicable to our patients, who seldom give them personal help and cooperation, and that one of the great benefits to be derived from this training is the development of the nurse's individuality and resourcefulness. The nurse is instructed to think for herself and use her own judgment, keeping in mind how she would wish a thing done were she the patient herself, or a member of her family. This is always a safe guide in the decision of any question.

It is also very difficult to do much bedside teaching for the reason that our patients are ever ready to take advantage of a nurse who appears not to know, and lose confidence if they discover a mistake is made. This does not prevent, however, a close observation of the nurse's work, and it is always easy to step in and assist, showing a better method, if need be, without a word of criticism, or taking up and diverting a conversation which it seems unwise to continue. With such an object-lesson, and a few explanatory words to the nurse apart, and more definite class-room teaching, the same mistakes are not likely to occur.

The ideal atmosphere to further improvement in mental illness is that of cheerfulness and confidence, and this can never be established where the nurse feels herself under criticism or distrust. There must be the greatest willingness on the part of the student to uphold and live up to her highest ideals and ethical standards, and the instructor must have confidence that she is doing so until her confidence is shaken. The nurses on entering are told that this is expected of them, and few have failed.

In a hospital where custodial care is the value set upon a nurse's work, training would be of little value, and did it consist simply in a few tricks or methods to be employed in decoying the patient to apparent submission or control, something to be considered a clever feat on the part of the nurse in overcoming a difficult situation, it would indeed be a waste of time for intelligent women; but the ideal nursing of mental patients is that which is re-educational, which requires the use of all the powers at the nurse's disposal, and which means self-development and control.

It is said that one's opinion is simply the expression of the light one has on a subject at a given time, and with new experiences that expression may completely change. We have expressed what we feel with reference to mental nursing, at the Quarter-Centennial of our training school, with only eighteen months experience; what we shall feel at the Bi-Centennial we do not know, but we feel confident that the underlying principle will remain the same, and that long before that period shall have been reached, mental training will occupy an important place in the curriculum of every progressive school of nursing.



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## THE ACCURATE CLINICAL STUDY OF BLOOD-SUGAR.

By SOLOMON STROUSE, M. D., Chicago,

ASSISTED BY

IRVING F. STEIN, M. D., and ALAN WISELEY, M. D.

(From the Department of Medicine, the Michael Reese Hospital and the Morris Institute for Medical Research.)

The necessity of using large amounts of blood and the inherent technical difficulties of determining the sugar content have stood in the way of extensive blood-sugar determinations. It is true that many estimations of blood-sugar have been published, but most of these have come from different observers in different laboratories, and with techniques not constant enough to permit of comparative criticism. Yet as the study of the normal and pathological in carbohydrate metabolism progresses, the need of methods allowing many determinations on the same person and not requiring the services of a specially trained chemist has been felt.

Ivar Bang<sup>1</sup> was perhaps the first to attempt to fill this need with a method meeting the requirements of the clinic and the demands of scientific accuracy. In this method only a few drops of blood are used, and the technique, once acquired,

can be performed by any clinician capable of performing the usual clinical laboratory routine. Since the publication of the original article, many workers have used the method, and Fitz<sup>2</sup> in this country has made an elaborate comparison of it with the Bertrand method. We did a considerable amount of work with the Bang technique, and feel that the procedure is extremely valuable; but, for reasons which will be discussed later, all the work which forms the basis of this paper has been done in an entirely different way.

One of the difficulties of sugar determinations with small amounts of blood has been that the normal content is so small as to cause too large a percentage error. To obviate this difficulty Kowarsky<sup>3</sup> has suggested the use of a copper solution containing a known amount of dextrose. The technique devised by him is based on two accurate chemical procedures



(1) the Michaelis-Rona method of de-albumenizing blood; and  
(2) the Bertrand copper reduction method of determining sugar.

The simplicity and apparent accuracy of the technique described by Kowarsky appealed to us as worthy of investigation for use in several studies on carbohydrate metabolism; and after only a few preliminary observations it was evident that by this method clinical observations on blood-sugar could be made with an accuracy even beyond our expectations. The details, as described by Kowarsky, have been considerably modified as our work progressed, and the description given below is of the technique as now practiced in our laboratory:

#### SOLUTIONS.

I. Copper sulphate (pure crystals).....	8.0
Dextrose (C. P.) .....	0.1
Water to.....	200.0
II. Pure Rochelle salts.....	40.0
Sodium hydroxide (sticks).....	30.0
Water to.....	200.0
III. Ferric sulphate.....	10.0
Concentrated sulphuric acid.....	40.0
Water to.....	200.0
IV. Potassium permanganate.....	1.0
Water to.....	200.0
V. Liquor ferri oxidati dialysati (Merck)...	5%
VI. Sodium fluoride.....	0.2% solution
Also pulverized Rochelle salts.	

Solution IV is used in a 10-fold dilution freshly prepared each day. It must first be standardized by titration against oxalic acid. The equivalent of the permanganate solution in copper is obtained by this titration. Kowarsky recommends the following technique of standardization. Exactly 0.1 gm. of ammonium oxalate is dissolved in 100 cc. of distilled water. To 10 cc. of this solution 2 cc. of concentrated sulphuric acid are added. The diluted permanganate solution is now titrated against this oxalic solution to a permanent red reaction. The number of cubic centimeters of permanganate solution is then made the denominator of a fraction of which the constant 8.95 is the numerator. The resulting figure equals the amount of copper in milligrams represented by 1 cc. of the permanganate solution.

#### APPARATUS NEEDED.

1. Several centrifuge tubes of ordinary laboratory size carefully calibrated and marked at the 0.5, 1.0, 5.0 and 10.0 cc. points. We have found it advisable to calibrate our own tubes, as several supposedly accurate tubes showed errors as high as 40 per cent.
2. An ordinary laboratory centrifuge.
3. Small Erlenmeyer flasks—capacity 50 cc.
4. An Allihn filter and suction pump.
5. Washed asbestos.
6. Burette of 10 cc. capacity divided into 1/20 cc. (0.05).
7. Volumetric flasks, 2, 3 and 5 cc. pipettes, etc., as found in any laboratory.

#### THE METHOD.

The sodium fluoride solution is placed in one of the calibrated centrifuge tubes up to the 0.5 cc. mark. In practically

all of our work the blood from a finger or ear prick was allowed to drop into the tube up to the 1 cc. mark, thus giving exactly 0.5 cc. blood. Water is then added up to the 5 cc. mark, a pinch of powdered Rochelle salts dropped in, the whole shaken and allowed to stand until the Rochelle salts are completely dissolved. Then the solution of dialyzed iron is added, making the total contents of the tube exactly 10 cc. It is now corked and vigorously shaken until the originally putty-like mixture becomes homogeneous and fluid. Centrifugalize for 3 to 5 minutes.

The dialyzed iron-blood mixture when removed from the centrifuge should show a water-clear supernatant fluid. Exactly 5 cc. of this clear fluid are used in the copper reduction, which is performed by mixing exactly 2 cc. of each of solutions I and II in the small Erlenmeyer flask and then adding the clear filtrate.

The reduction process must take place on an asbestos mesh over a *low constant* flame and must continue exactly 3 minutes from the time boiling starts. While this is going on, the asbestos filter is prepared and washed, and the suction pump thereby tested out. After 3 minutes boiling the Erlenmeyer is rapidly cooled under the cold water faucet *without shaking*, and the contents immediately poured on the filter. The reduced copper oxide remains in part adherent to the sides of the Erlenmeyer flask and to the surface of the asbestos filter, and both flask and filter must be carefully washed several times with distilled water.

The funnel is then disconnected from the filtrate flask containing the unreduced copper sulphate and the washings. The filtrate flask is thoroughly cleansed with distilled water and again connected up with the funnel. Three cubic centimeters of the acid ferric sulphate solution are now added to the original Erlenmeyer flask, care being taken that it is well distributed over the whole of the inside of the flask. The contents of the flask are then poured upon the asbestos in the funnel and allowed to stand 1 minute. By this time all the reduced copper will have been taken into solution, and the suction pump is again started. The Erlenmeyer flask is carefully washed 3 or 4 times with 3 to 5 cc. of distilled water, each washing being poured into the funnel of the suction pump. The contents of the filtrate flask are then titrated against the permanganate solution diluted 1:10, until a definite pink color persists.

The results are easily figured. The amount of permanganate solution in cubic centimeters is multiplied by the constant for this solution (as previously determined) and its equivalent in milligrams of dextrose obtained from the following table:

Copper.	Sugar.	Copper.	Sugar.	Copper.	Sugar.
1.95	1.0	3.50	1.8	5.00	2.6
2.15	1.1	3.70	1.9	5.20	2.7
2.35	1.2	3.85	2.0	5.40	2.8
2.55	1.3	4.05	2.1	5.60	2.9
2.75	1.4	4.25	2.2	5.75	3.0
2.90	1.5	4.45	2.3	5.95	3.1
3.10	1.6	4.65	2.4	6.15	3.2
3.30	1.7	4.80	2.5	6.35	3.3



But it must be remembered that 200 cc. of the original copper solution contained 100 mg. of dextrose, so that the 2 cc. used in the test contained 1 mg. of sugar. When this is subtracted from the sugar obtained, we have just the amount of sugar in the blood. Originally 0.5 cc. of blood was used, but only half the total (5 cc. filtrate) is used in the test, so that the amount of sugar represents that in 0.25 cc. of blood. From this it is easy to determine the amount in 100 cc. of blood, by multiplying by 400.

It is well here to call attention to the fact that for the titration to be successful the filtrate, after the addition of the dialyzed iron and centrifugalization, must be water clear. Two factors occasionally enter to prevent this. At times not enough Rochelle salts is added, and at other times there is insufficient iron. To obviate the latter possibility we have been in the habit of using 5 to 6 cc. of the iron solution. Students of the original Kowarsky article will note that he advises the use of "Merck's liquor ferri dialysati oxidati diluted with an equal amount of water." However, the liquor put out in this country is a 5 per cent solution, and must be used in its whole strength. Dilution according to Kowarsky's technique will spoil the test. At times the iron solution does not seem to maintain a constant strength, and often in the case of a new bottle it will be found necessary to use a little more or a little less than 5 cc.—always being careful, however, that the total equals 10 cc.

This whole procedure from beginning to end can be carried out in 15 minutes. Practically no special apparatus is required. The blood can be obtained in the hospital ward or the office, put in the tube with the fluoride solution and water and carried to the laboratory to be finished. Almost any physician (who knows the essentials of quantitative chemical analysis) after seeing the test performed a few times can carry it out himself. The chemical principles on which it is founded are sound and proved, and the only criticisms lie in its technical execution as outlined by us, and in the possible errors from the use of so small an amount of blood.

The measuring of the blood seems crude and inefficient, and we felt strong doubts as to whether the centrifuge tube method could possibly be accurate enough. Originally it was adopted temporarily by us in place of the "fläschenformige Röhrchen" of Kowarsky, which could not easily be obtained. Although we were decidedly of the opinion that the use of the tubes as described could not possibly give accurate results, a series of controlled experiments proved that our theoretical objections must fall before the proof of actual results. But even if others find this part of the technique inefficient, it can offer no logical objection to the value of the method. Certainly a more scientific procedure would be the weighing of the centrifuge tube just before and just after the blood has been placed therein.

The method of de-albumenizing the blood has received so much study and has met with the approval of so many chemists that we need not further discuss it here. Likewise the Bertrand sugar titration has met with general approval. As a

matter of fact the control tests of the copper-dextrose solution, made constantly in the course of the work, gave convincing evidence that all the sugar in solution was quantitatively recovered by this technique.

Many statements have been made as to the impossibility of obtaining accurate results in any method in which less than 5 or 10 cc. of blood are employed; but on the whole these objections have come from men who have not tried to determine blood-sugar with small amounts of blood. Bang and his followers are convinced of the accuracy of the new Bang micro-method, in which only a few drops of blood are used, and a critical study of the brilliant results already published by the use of his technique fails to reveal anything less scientific than those published by workers using larger amounts of blood. On the other hand, methods such as Bang's or the one here described open up fields of scientific investigation absolutely impossible where large amounts of blood are necessary. The effect of withdrawing blood on the subsequent determinations of blood-sugar, the effect of the excitement of more than one venopuncture have been proved beyond a doubt for laboratory animals; and surely the emotional instability of sick patients is a factor which must be considered.

No better illustration of the need of a "clinical" method can be cited than the obscurity surrounding the definition of normal blood-sugar. One finds in the literature figures varying from 0.04 to 0.12 per cent, but, until Jacobson<sup>4</sup> studied the subject by serial determinations on single individuals with special reference to the effect of diet and of ordinary physiological stimuli, the significance of these limits was not apparent. Furthermore, in the field of carbohydrate metabolism and especially in the obscure interrelations between glycemia and glycosuria, it has been definitely shown that animal experiments cannot be translated into human physiology and pathology; and this fact adds further reason to the need of investigating methods that simplify the study in man.

It has seemed to us that the method we have described fills all the requirements of an absolute science as well as those of the clinic, and is therefore an ideal method for the pursuit of extensive investigations of the numerous problems of blood-sugar. When compared with Bang's micro-method, it is seen that it requires more blood, but in this respect only does it compare unfavorably. The final titration with the Bang method, in which a purple blue must be differentiated from a green blue has, in our hands, at least, proved a much more difficult problem than the simple end-point in permanganate titration. Also the necessity of working in an atmosphere of carbon dioxide complicates the Bang technique, and the addition of a known amount of sugar in Kowarsky's method makes the percentage error less.

#### THE NORMAL BLOOD-SUGAR.

The first problem investigated by us was one which seemed of fundamental importance and without which any subsequent studies would be futile, viz., the problem of normal blood-



sugar and its variations under normal conditions. We quote some of the published figures for normal blood-sugar in man:

Author.	Percentage.	Method.	Number of determinations.
Naunyn <sup>5</sup>	0.07 -0.10	Abeles.	4
Klemperer <sup>6</sup>	0.08 -0.11	.....	..
Liefman & Stern <sup>7</sup>	0.07 -0.11	Knapp.	20
Hollinger <sup>8</sup>	0.07 -0.10	Knapp.	10
Bang, I. C.	0.10 -0.11	Micro-method.	3
Leire <sup>9</sup>	0.06 -0.11	Micro-method.	17
Frank <sup>10</sup>	0.08 -0.11	Bertrand.	15
Oppermann and Rolly <sup>11</sup>	0.062-0.088	Bertrand.	15
Kowarsky, I. C.	0.05 -0.11	Kowarsky.	20
Freund and Marchand <sup>12</sup>	0.055-0.12	Frank.	20
Purjesz <sup>13</sup>	0.045-0.087	Bertrand.	10
Jacobson, I. C.	0.09 -0.116	Micro-method.	14

It will be seen from the above statistics that there are wide variations in the amount of sugar as found by different workers with different methods. Some of the authors give details as to the conditions under which the determinations were made, but most of the "normals" are indefinite. Furthermore, the different techniques and the varying amount of blood used in individual series would make comparisons unprofitable, so that on the whole it seems difficult to explain the variations. The likely causes would be the varying conditions of the experiments, the fact that in one series the studies were made on a fasting stomach and in another after a meal, that the effect of diet, of exercise, of other diurnal variations in any human being which influence sugar mobilization, was not considered. It seems almost a foregone conclusion that a carbohydrate-rich diet should, even in a normal being, influence the amount of circulating sugar and that the diet factor must be considered in any study of the normal. Yet Tachau<sup>14</sup> claims that in 15 normals who were given 100 gms. of dextrose on an empty stomach the blood-sugar was no higher one hour after the ingestion of the sugar than before. However, he failed to make determinations on each individual before the dextrose was given and, as we shall show later, such determinations are necessary if one is to interpret results correctly. He also made no determinations before the end of an hour, whereas Jacobson claims that a hyperglycemia ensues within half an hour after the feeding of dextrose to normal persons.

Jacobson also showed conclusively that after an ordinary meal the sugar content of the blood reached a higher point than before the meal, and that this rise was due entirely to the carbohydrate content of the food. In 15 persons receiving 100 gms. of dextrose on an empty stomach before breakfast he invariably found a hyperglycemia usually within half an hour after ingestion, while of 14 persons receiving 167 gms. of bread, all reacted with hyperglycemia and 6 with glycosuria. The only difference between the effect of dextrose and of starch was in the rapidity of the rise and fall of the sugar curve, undoubtedly due to the differences in the rate of absorption. Protein and fat had no such effect, and the giving of fat with the starch produced a milder hyperglycemia than that produced by the starch alone. Leire also claims to have found a rise in blood-sugar after an ordinary meal.

In order that we might have a clearer understanding of the actual meaning of the word "normal" as applied to blood-

sugar, we planned experiments in which the same individual should be the subject of studies under varying conditions of an active normal life. Perfectly healthy young men and women were used and we planned to plot the normal curve, beginning early in the morning just after rising, after breakfast, and before and after dinner. All post-prandial determinations were made one hour after eating, and in several cases the studies were repeated on the same person either the next day or in a few days after the original work. Obviously such a scheme can be followed only when small amounts of blood are used.

It was soon found that a very definite curve could be plotted for every individual and that, although the exact height of the figures varied slightly under similar living conditions, the curves of all normal individuals followed similar lines. It was also evident that the most important factor influencing the daily changes in blood-sugar was the carbohydrate in the diet. The lowest normals were usually obtained in the early morning; after breakfast there was a rise followed by a fall and a second rise after dinner. In persons who took no carbohydrate such a curve was not followed, and practically the same figure was obtained all day. In many instances, when we received the blood marked in such a way as to make it impossible to know its source, we were able to state that the person had eaten no starches; and in this way an interesting control over the accuracy of the method was accidentally developed. All experiments were carried out in the same manner. Each day's work was planned in advance, the assistants procured the blood and gave the specimens to the writer for the actual sugar determinations, which were thus carried out in an entirely objective manner. Occasionally, instead of taking the ordinary mixed diet the subject would go on a protein-fat régime, and in every instance the writer could diagnose the "mistake."

The work on the normal individual was supplemented by work on diabetes (about 25 determinations) and on miscellaneous hospital patients (also about 25 determinations). But as these titrations will form the subject of subsequent communications they will be mentioned in this report only when needed to force comparisons.

TABLE I.

Time.	Min.	Max.	No. determ.	Average.
Before breakfast.....	0.04	0.088	6	0.066
After breakfast, 1 hr....	0.08	0.124	5	0.103
Before dinner.....	0.04	0.096	15	0.066
After dinner, 1 hr.....	0.068	0.140	35	0.091
Totals .....	0.04	0.140	61	0.084

These figures are collected to give a general view of blood-sugar variations. Of more importance it seems to us are the individual variations. Some of these are shown in the following table:

TABLE II.

Patient.	Before breakfast.	After breakfast.	Before dinner.	After dinner.
I.	0.04	0.124	0.084	0.092
II.	0.088	0.140	0.088	0.104
III.	0.052	0.08	0.096	0.104
IV.		0.092	0.04	0.076
V.		0.08	0.06	0.08



This table shows quite definitely that there is not a fixed value for the "normal" blood-sugar; and that the "normal" varies for each individual, depending on the diet. The variations are between rather wide limits and to obtain any true idea of the behavior of an individual toward sugar transportation, it is necessary to determine the sugar before and after an ordinary meal. The only difference in blood-sugar between the normal and the diabetic organism is one of degree. The diabetic curve is identical with the normal curve, but the low figures are not obtained and the variations are higher. On the other hand, in mild diabetes the blood-sugar on a fasting stomach may be within normal limits. Therefore, comparisons of single blood-sugar determinations on individuals, either from the standpoint of diagnosis or of treatment, are without value.

One most interesting case will illustrate the necessity of determining the curve of blood-sugar. A young man had for about 30 days multiple furuncles which despite active surgical intervention refused to heal. Physical examination showed a very healthy man with no cause for the persistence of the furuncles. The urine examination for several days showed the following: 24 hour specimen, amount 2500 cc.; s. g. 1012, no albumin, no sugar; microsc. exam., negative; certainly not the kind of urine to make one suspect a disturbance of carbohydrate metabolism. Nevertheless because the persistence of the furunculosis suggested the behavior of a diabetic and because the patient's mother had died of diabetes, we thought it worth while to study his blood-sugar curve. On two days the tests were made and the curve was plotted with the patient on the same diet as was used in our normal determinations. The blood-sugar in the early morning on an empty stomach was 0.06 per cent; 1 hour after breakfast 0.14 per cent, 1 hour after dinner 0.168 per cent; showing a definite alimentary hyperglycemia. Dr. Eisendrath, the surgeon asked us to assume charge of the case, and a strict carbohydrate-free diet was ordered. In 24 hours the furuncles then present had begun to heal; within 48 hours no new ones had developed and by the end of a few days all the old ones were healed. In this case the test, as applied by us, was of distinct therapeutic value, whereas had we done only a single examination without relation to diet we might have missed the post-prandial hyper-

glycemia. Incidentally, such a case with a diabetic family history and also with urine suggestive of chronic nephritis induces speculation on two interesting scientific problems (1) the early changes in diabetes mellitus and (2) the interrelations between glycemia and glycosuria. In the study of both of these problems the basic facts on normal blood-sugar here laid out and the technique here described have already been employed.

#### CONCLUSIONS.

1. The Kowarsky method of determining blood-sugar, as modified by us, affords an efficient and accurate means of studying blood-sugar in man.
2. The normal blood-sugar, as shown by a study of 61 determinations, varies from 0.04 per cent to 0.12 per cent (in one instance 0.14 per cent) with an average of 0.084 per cent.
3. These variations are due to the varying factors in the ordinary day of any normal individual—especially to the diet factor.
4. Carbohydrate in the diet raises the blood-sugar.
5. The blood-sugar of a normal man describes a curve reaching its lowest limits before breakfast and before dinner, and invariably showing a rise one hour after meals.
6. Blood-sugar determinations to be of any value must be performed before and after an ordinary meal containing carbohydrate.

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## CHORIO-EPITHELIOMA OF THE TESTICLE.\*

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Teratomatous growths of the testicle include certain tumors which closely resemble chorio-epithelioma in women. In 1878 the first of these was described by Mallassez and Monod and designated a *sarcome angioplastique*, but Schalgenuhauser in 1902, noting the similarity between these tumors and chorio-

epitheliomata of trophoblastic origin, first expressed the view that both were in reality identical. Wlassow in the same year also noted the similarity between these two neoplasms, but apparently attached no importance to it. Subsequently, cases of chorio-epithelioma of the testicle have been recognized from time to time and at present 46 instances have been recorded. Some of these tumors have been the subject of detailed study and discussion; others have been reported briefly and with

\* The case here reported was observed and the autopsy performed at the Pennsylvania Hospital, Philadelphia.



fragmentary clinical and pathological notes. A few cases are reported in a too incomplete form to be of value. To these cases collected from the literature I wish to add another and also to call attention to several features apparent upon study of the material now at hand.

Our patient was admitted at the Pennsylvania Hospital (Hosp. No. 826) to the service of Dr. J. C. Wilson, to whom I am indebted for the clinical notes.

T. S., an Irishman 26 years of age, a worker in a salt factory, was admitted on June 6, 1911, in a semi-stuporous condition. His family and past history were negative. The history of the present illness, obtained from a relative, follows: Five days before admission the patient returned from work complaining of severe cramp-like abdominal pain. Several times during that evening he vomited a brownish-red material, and two days later again vomited similar material. He had severe headache continuously, had been rather stupid, and his eyesight had become poor. At times the abdominal pain appeared to be more severe in the epigastrium, but as a rule it was general and not localized. His appetite was poor.

*Physical examination.*—A large, well-built, well-nourished man, who lies in a semi-stuporous condition, and answers questions slowly and unintelligently. The eyelids are closed most of the time, but at intervals he appears quite uncomfortable and groans. The tongue is protruded in the mid-line and is not tremulous. The teeth are in good condition and the fauces are not congested. The chest is large and well formed. The mammary glands are rather prominent, the left nipple is enlarged and is surrounded by a fairly well-developed glandular base. Pressure upon the breasts expresses a few drops of colostrum-like fluid. The heart and lungs are negative except for a small area of impaired resonance in the left axillary region. Here the breath sounds are roughened. The abdomen is full and soft, but not distended; there is slight, general tenderness on palpation, but no muscle rigidity. The liver and spleen are not enlarged. The scrotum is occupied by a large firm ovoid tumor of the right testicle which is round, tense, dull to percussion and does not transmit light. The extremities are well developed and normal. The patellar reflexes are not obtained. The pulse is of good volume and moderate tension, regular in rate and rhythm; the vessel-wall is soft. The urine has a specific gravity of 1033, is reddish brown and slightly turbid, acid, contains no albumin or sugar and on microscopic examination is negative. Wassermann reaction negative. Temperature, 99° F.

*Progress.*—For two days after admission the patient's condition remained unchanged. On the third day he became more restless and noisy and groaned frequently. During the night he had three dark, tarry bowel movements. He seemed very uncomfortable and apparently had pain in his head and abdomen. About 12 hours later he vomited approximately 1000 cc. of blood which was partially clotted.

During the following night he was restless and the next morning vomited a small quantity of blood clots, but no fresh blood. Again he complained of pain in his head and abdomen. During the day he passed by the bowel a small amount of changed blood. The leucocytes were 25,000 with 70 per cent of polymorphonuclears. A blood culture was sterile. The following day (the fifth after admission) his condition remained practically unchanged, except that the temperature rose several degrees. In the evening he died. The underlying pathological condition was not suspected, and the clinical diagnosis was "gastric hemorrhage."

*Autopsy*, June 12, 1911 (A 1441): 11 hours after death.

*Anatomical diagnosis.* *Chorio-epithelioma of right testis with metastases to brain, liver, kidneys, stomach, peritoneum and thyroid gland. Ulceration of metastatic nodule in gastric mucosa*

*with extensive hemorrhage into the stomach and intestines. Cloudy swelling of heart, liver and kidneys. Acute splenic tumor. Hypertrophy of breasts.*

The body is that of a large, well-nourished white man 178 cm. in length. The pupils are of moderate size and equal. No discharge from the ears, nose, or mouth. Both breasts are somewhat enlarged and a thin colostrum-like fluid can be expressed from the left nipple. There is a swelling of the right side of the scrotum measuring 7 x 7 x 11 cm. The extremities are not edematous.

The serous surfaces of the *peritoneal cavity* are covered with bloody fluid and there is a similar fluid in the flanks. In the pelvis there are probably 100 cc. of thick bloody fluid that has a purplish color. Attached to the upper portion of the sigmoid colon is an irregular mass, 2 cm. in diameter. Its surface is somewhat lobulated and dark red in appearance, with irregular areas of reddish grey. On section it is dark red and is traversed by an occasional greyish trabecula. The mass is attached to the sigmoid in two places by a band of connective tissue, 2 cm. in length. The omentum shows small lobules of fat and in places is quite dark in color. The appendix is normal. The intestines are moderately filled with fluid and are somewhat discolored, but when the bloody fluid is wiped away, the serous surfaces appear smooth. The liver lies well behind the costal margin and the diaphragm reaches to the third rib on the right and the third interspace on the left. The gall-bladder appears normal.

*Thorax.*—On removal of the sternum the lungs collapse. The pleural surfaces are pale grey and everywhere free from adhesions. On the anterior surface of the lungs there are some small raised firm areas which are slightly darker than the surrounding pulmonary tissue. The pericardial surfaces are smooth and glistening and the cavity does not contain any excess of fluid. The *heart* weighs 310 grams and measures 12 x 9 x 5 cm. The pericardial surface is smooth and there is a considerable amount of subepicardial fat. The organ shows no gross abnormalities. The coronary arteries are delicate and patulous. The *right lung* weighs 460 grams. It is small, collapsed, and pale grey in color. The pleural surface is smooth and glistening. Beneath the pleura and through the pulmonary substance there are scattered rather firm spherical dark red nodules varying in size from 5 mm. to 15 mm. Section of these areas shows a dark red hemorrhagic tissue through which run irregular grey trabeculae. Some of the small nodules on section show smooth reddish-grey cut surfaces and only a slight amount of hemorrhage, while the larger ones frequently reveal an irregular shaggy-walled central cavity containing hemorrhagic material. The lung is dry and pale. The pulmonary artery contains elastic post-mortem clots and appears normal. The bronchial lymph nodes are small.

The *left lung* weighs 410 grams and is similar to the right. In addition to the small, dark red nodules scattered through the lung there is found on the diaphragmatic surface a large spherical nodule, 6 cm. in diameter, similar in appearance to the smaller tumors. The bronchi at the root, the bronchial lymph nodes and the pulmonary artery are similar to those of the opposite lung.

The *spleen* weighs 190 grams and measures 13 x 9 x 5 cm. The consistency is soft on section and the pulp is reddish purple in color. The Malpighian bodies are small. No tumor nodules are found. The *liver* weighs 1460 grams and measures 27 x 20 x 5 cm. The surface is smooth and reddish brown in color. Occasionally there are seen irregular dark red areas beneath the capsule. These areas measure from 3 to 10 mm. in diameter and are hemorrhagic. On section the liver is light brown and small nodules are found scattered through the liver parenchyma, similar to those noted beneath the capsule. The *gall-bladder* is of moderate size and contains some yellowish bile. The *kidneys* together weigh 280 grams. The right measures 11.5 x 6 x 4 cm. The capsule strips easily, leaving a pale brown surface. At the upper pole there is a small, dark red nodule, 5 mm. in diameter, similar



to those described in the other organs. The cortex is very pale, but the markings appear regular. The Malpighian bodies are just seen as minute points. The left kidney measures  $13 \times 5 \times 4$  cm. A nodule 1.5 cm. in diameter is found on the posterior portion of the kidney just below the hilum. This is dark red on section and similar to the areas noted elsewhere. Otherwise this kidney resembles its fellow. The *adrenals* are of moderate size. The cortex is very pale and opaque, otherwise they appear normal. The *urinary bladder* and *prostate* show nothing noteworthy.

The *left testis* measures  $3 \times 2 \times 1.5$  cm. and on section appears normal. The *right testis* measures  $12 \times 8 \times 7$  cm. and is rather firm in consistency. On section the tissue is for the most part hemorrhagic and necrotic. Some fairly large areas are seen which are dark red in color and friable. Through these grey linear streaks run irregularly. Other softened areas contain necrotic brownish material. No cysts are seen, nor are any areas found which are not dark red and hemorrhagic.

The *stomach* is moderately dilated and filled with dark reddish-brown material. In the fundus near the lesser curvature there is a nodule measuring 2.5 cm. in diameter, which is situated in the mucosa or submucosa and is freely movable. The surface of this nodule is quite irregular, dark red, and ulcerated. On section it appears exactly similar to the hemorrhagic metastatic nodules found in the other viscera. The mucosa around this is very slightly congested. The *pancreas* is firm and pale on section. It shows no gross lesions. The *duodenum* is pale and appears normal. In the *jejunum* and *ileum* there is a large amount of semi-fluid, bright red hemorrhagic material; while in the upper part of the intestines this material is of a bright red color, in the lower part of the ileum it is dark red. The lymphoid tissue is more prominent than usual. The *large intestine* contains dark greyish-black tarry material. When this is wiped off, the mucosa shows no gross lesions. Near the splenic flexure there is a large mass, measuring  $15 \times 7 \times 6$  cm., which is loosely attached to the serosa and does not involve the wall of the gut. It is covered by fat and connective tissue and on section is similar to the testicular tumor.

The *tongue*, *tonsils*, *pharynx*, *larynx*, and *trachea* are pale and show no gross lesions. The *thyroid gland* is of moderate size, firm, and on section is pale brown in color. The right lobe contains a dark red metastatic nodule, about 2 cm. in diameter.

The *brain* weighs 1400 grams. On removing the brain, the pia shows no excess of fluid. The cortex over the right median frontal convolution shows an irregular area of subpial suffusion of blood measuring about  $2 \times 3$  cm. This is just in front of the anterior central convolution. The left occipital lobe at its posterior and lower portions is firmly adherent to the dura over an area about 5 cm. in diameter. On removing the brain, there is exposed in this portion a large, rather firm dark red mass, 6 cm. in diameter. On section this mass is exactly similar to those found in the various viscera. Section through the right frontal lobe shows beneath the area of subpial hemorrhage another metastasis  $3 \times 2 \times 2$  cm. This has involved the deeper portion of the cortex beneath the area described, but for the most part replaces the white matter. Sections of the remaining portion of the brain show nothing unusual.

Smears from bloody fluid in the peritoneum show neither pus cells nor bacteria.

Cultures from the heart's blood and spleen remain sterile.

*Microscopic examination. Tumor of right testicle.*—Sections were made through various portions of the growth and each block was studied, though one scarcely differed from another. By far the larger part of all the sections was occupied by areas of hemorrhage and fibrin, with here and there masses of pink-staining cells indefinitely outlined. Occasionally small masses of well-stained tumor cells were scattered through the structureless hemorrhagic tissue. At no point was there evidence of tubules, nor were any blood-vessels found.

Most of the sections, particularly those taken from the edges of the tumor mass, show areas where the tissues stain well, and the structure of the tumor can be distinctly seen. Large polygonal cells of the Langhans' type are massed about irregular blood spaces. Lining the blood spaces and separating them from the Langhans' cells are flattened multinucleated syncytial masses. The Langhans' cells vary somewhat in size and have an irregular polygonal shape, although frequently the cell outline is not clearly made out. The protoplasm is granular and shows a well-marked vacuolization which in some of the cells is so marked that the nucleus appears surrounded by a clear zone, outside of which the cell membrane is seen. The nuclei also show some variation in size and shape, but most of them are round, oval, or vesicular, and rather poor in chromatin. Each shows a distinct, fairly deep-staining nucleolus. Mitotic figures are common. There is no demonstrable intercellular substance, and no definite blood-vessel. Many parts of the tumor show multinucleated, rather basophilic, masses of protoplasm. Occasional giant cells of this character are found among the Langhans' cells, but their most common location is in sheets between the Langhans' cells and the large, irregular blood spaces which honeycomb the tumor, thus occupying the same position with relation to the Langhans' cells and the blood spaces that syncytium does in normal placenta.

The large blood spaces are filled with red corpuscles, fibrin and serum, with leucocytes scattered through the mass. No intercellular connective tissue can be demonstrated.

Tissue derived from the other embryonal layers is not found in any section of the tumor.

Sections through the metastatic nodules in the organs show the same type of tumor as the original growth. The smaller nodules show much less necrosis and the tumor elements are well preserved. Multinucleated syncytial tissue is found much more commonly and almost always lines the irregular blood spaces in flattened sheet-like masses. One section of kidney shows, near a fairly large metastasis, two medium-sized blood-vessels, in each of which lies tumor tissue surrounded by blood. These tongue-like tumors have evidently been continued through the lumina of the vessels from the larger metastatic mass and have been cut in cross section.

The *left testicle* appears normal and the tubules show well-marked spermatogenesis.

*Heart.*—The pericardium and muscle are normal.

*Lungs.*—The pleura is normal. For the most part the pulmonary alveoli contain air and appear normal, although occasionally patches of early broncho-pneumonia are seen. Sections of the dark red nodules noted in the gross description show metastases from the testicular tumor.

*Spleen.*—The Malpighian bodies appear normal, but are somewhat irregular. In the spleen pulp there are large numbers of polymorphonuclear leucocytes. There is no increase in the trabeculae.

*Liver.*—The parenchymatous cells are swollen and granular. There is no increase in the portal connective tissue. Sections of the metastatic tumor nodules show the same appearance as described in similar nodules in the lung, except that the syncytial layer is more easily distinguished. At the edges of the nodule the tumor cells are invading the surrounding hepatic tissue.

*Kidneys.*—The epithelium of the convoluted tubules is somewhat granular and the cells are swollen. The glomeruli appear normal and there is no increase in interstitial tissue. A metastatic tumor nodule in the cortex shows the same appearance as that described elsewhere. The *adrenals* appear normal.

*Thyroid gland.*—The acini are fairly regular and contain colloid. The epithelium is flat. One section shows a large metastatic tumor nodule.

*Left mammary gland.*—The sections show masses of fat with an abundant fibrous connective tissue and fairly numerous tubules lined with epithelium. These are frequently isolated, but groups



of five or six are occasionally seen. Their size varies considerably, some being about the size of small non-lactating mammary acini and others larger—1.5 x 0.2 mm. Most of the ducts are somewhat irregular in outline and there is a tendency to an infolding of the epithelium. They are lined with a single layer of columnar epithelium, which shows a proliferation with an occasional mitotic figure near the basement membrane. In the lumen there are

The 47 cases below present a number of clinical features which may be summarized as follows:  
The *age* of the patients varied from 16 to 46 years, but the large majority of cases occurred in individuals between 20 and 40 years old. Among the cases in which the side involved was mentioned, there was a slight predominance of involvement of

TABLE SHOWING COLLECTED CASES OF CHORIO-EPITHELIOMATA OF THE TESTICLE.

No.	Reporter.	Age.	Side.	Duration.	Result.	Other Teratomatous Growths in:		Remarks.
						Tumor.	Metastases.	
1	Mallassez & Monod.	27	Left.	1 yr.	Death.	None.	None.	Other teratomatous elements not looked for.
2	Carnot & Marie.	37	"	10 mos.	"	"	"	" " " "
3	Dopter.	28	Right.	6 mos.	"	"	"	" " " "
4	Wlassow.	....	....	....	....	"	....	No clinical data.
5	"	....	....	....	....	Present.	....	" " " "
6	"	....	....	....	....	"	....	" " " "
7	"	....	....	....	....	"	....	" " " "
8	Schlagenhauser.	43	Left.	?	Death.	"	None.	Interpreted as hydatidiform mole.
9	Breuss & Schlagenhauser.	40	Right.	2½ mos.	"	"	"	No clinical data.
10	Carey.	....	....	....	....	"	Present.	
11	Schmorl & Steinert.	22	Left.	....	Death.	"	....	
12	Schmorl.	17	....	....	....	"	....	
13	Steinhaus.	32	Left.	6 mos. +	....	"	....	
14	Risel.	20	"	....	....	....	....	
15	"	35	....	....	Death.	....	Present.	Original tumor not examined.
16	Emanuel.	26	Left.	4 mos.	"	Present.	....	Atypical forms present.
17	v. Hanseemann.	28	Right.	....	....	....	Present.	Original tumor not examined.
18	Askanazy.	24	Right.	1 yr.	Death.	None.	....	Atypical forms present.
19	Scott & Longcope.	45	"	2 mos. +	"	"	None.	Tumor of undescended testicle.
20	Dillman.	32	Left.	4 mos. +	"	Present.	"	
21	Frank.	40	?	2 yrs.	?	None.	....	
22	"	16	Left.	2 mos. +	?	Present.	....	Atypical forms present.
23	Sternberg.	26	Right.	1 yr., 2 mos.	Death.	None.	None.	
24	Chevassu.	30	Left.	3 mos.	?	"	....	
25	Lawrence.	....	....	....	....	Present.	....	
26	Reinhold.	30	Right.	7 mos.	Well?	"	....	Well 5 mos. after operation.
27	Bernstein.	34	Left.	4 mos.	Death.	None.	None.	
28	"	29	Right.	....	"	"	"	
29	Bonney.	....	....	....	....	"	....	
30	"	....	....	....	....	Present.	None.	
31	Orton.	38	Left.	5 mos.	Death.	None.	"	
32	Mönckeberg.	19	"	10 mos.	"	"	"	
33	"	34	Right.	....	?	"	....	
34	"	Young.	....	....	Death.	Present.	None.	
35	Chuvin.	20	Right.	6 mos.	"	None.	"	
36	Taylor.	28	Left.	8½ mos.	"	Present.	"	
37	Fink.	35	....	....	"	None.	....	
38	Gruner.	25	Left.	5 mos. +	?	Present.	....	
39	Glaserfeld.	23	"	2½ yrs.	Death.	"	None.	
40	Sigl.	34	Right?	6½ mos.	"	None.	"	Several congenital abnormalities.
41	Conforti.	46	Left.	2½ yrs.	"	"	"	
42	Zenoni.	32	Right.	....	"	"	"	
43	Marcora.	29	Left.	1 yr.	"	Present.	....	
44	Keenan.	20	Right.	7½ mos.	"	None.	None.	Tumor involved only the epididymis.
45	Tirumurti.	35	"	2 mos.	"	"	"	Tumor of undescended testicle.
46	Warthin.	35	"	....	"	Present.	"	Hyperplasia of breast.
47	Cooke.	26	"	?	"	None.	"	" " "

granular detritus, degenerating cells and cell shadows. Sections from the right breast unfortunately were not taken.

*Alimentary canal.*—Sections through the ulcerated nodule in the gastric mucosa show a considerable amount of necrotic and hemorrhagic tissue and some areas with typical chorio-epitheliomatous structure. No lesions are noted in the intestinal mucosa.

*Brain.*—The metastatic nodules are quite similar in structure to those found in the other organs.

The accompanying table shows the principal features of all the cases that have been reported.

the left testicle, the ratio being 6 to 5. In two cases an undescended testicle was the seat of the tumor.

The duration of the disease varied greatly. In most of the cases, it was less than a year; the longest was 2½ years and the shortest 2 months. Invariably the prognosis was grave. In 29 cases a fatal termination was specifically mentioned. One patient appeared to be well 5 months after operation. In the remaining 17 the post-operative result was not given.

The *local symptoms* consisted of testicular enlargement of



varying degree unaccompanied by discomfort, or at most by dull dragging pain. As would be expected, the general symptoms varied with the localization of the metastatic tumors. By far the most common were referable to the secondary pulmonary growths, viz., hemoptysis and dyspnoea. A common finding was enlarged abdominal lymph nodes, which could be palpated and in some cases caused pressure symptoms. In several cases fatal hemorrhage occurred from metastases in the lungs, stomach or intestines. In two cases hypertrophy of the breasts with secretion of colostrum-like fluid was observed, but in none of the others was reference made to the condition of the breasts. Cachexia with loss of weight and strength was remarked in the terminal stage of all the cases.

Obviously, chorio-epithelioma of the testicle has no distinctive clinical feature and differs very slightly from other malignant testicular growths, except that occasionally it has been accompanied by hyperplasia of the breasts. Metastases become disseminated early and usually the patient is beyond hope when a physician is consulted.

Typically in their chorio-epitheliomatous portions the tumors are very hemorrhagic and necrotic. Microscopically the living tissue is composed of large, faintly staining polygonal cells of the Langhans' type and, among these, multinucleated islands of syncytium are scattered. Numerous irregular blood spaces, frequently lined with flattened syncytial plates, are distributed through the Langhans' cells. On the other hand, in a few instances the chorio-epithelioma has consisted of isolated cells or groups of cells which stain more deeply and are very irregular; occasionally, no multinucleated masses are present. Three cases have shown the type of growth first mentioned, in some part of the tumor, while in other parts the cells and arrangement have presented variations of an exceptional nature. For example, besides the usual alveolar arrangement, the Langhans' cells are found in a more independent proliferation consisting of duct-like and complex papillary forms lining cystic spaces.

In addition to the chorio-epitheliomatous portions, teratomatous or teratoblastomatous elements have been found in the original tumor in about half the cases and, in three, other structures beside the chorio-epithelioma have been found in metastases, although the latter have not shown malignant characteristics. Therefore, it seems scarcely open to doubt that these tumors are derived from pluripotential cells. While derivatives from more than one embryonal layer have not been found invariably, this may be due to the fact that they were present in such small amount that serial sections would have been necessary to demonstrate them; or, as seems more probable, the malignant chorio-epitheliomatous tissue may have invaded and destroyed the other elements just as in most cases it has destroyed the testicular tubules.

Perhaps the most interesting feature of the case I have reported is the hyperplasia of the breast with the secretion of a colostrum-like fluid—a phenomenon which Warthin also has observed. In Warthin's case, after the surgeon had removed the testicular tumor, the breast decreased in size, but later, during the development of general metastases, the hyper-

plasia became more marked than it had ever been. Unfortunately, in no other case has a note been made regarding the condition of the breasts.

At present the more plausible theories of mammary secretion ascribe the activation of the glands to a substance (hormone?) originating from one or more of the three sources—the embryo, the corpus luteum, and the placenta. There is evidence in favor of each view, but none rests on a firm basis. In the cases observed by Warthin and myself the association of functional activity of the breast, with a placenta-like tumor present in the body, suggests that a substance may occur in chorio-epitheliomata and probably also in the normal placenta which activates the mammary glands.

The precise nature of these testicular growths has been disputed and the opinions expressed regarding their origin have varied widely. It has been difficult to account satisfactorily for teratomatous and teratoblastomatous testicular tumors which contain trophoblastic elements. The three possibilities which immediately suggest themselves are that they arise (1) from the interstitial cells of the testicle; (2) from misplaced multipotential cells included in the organ during embryonic development; or (3) from the spermatogenic cells themselves.

A few observers have favored the endothelial origin of these tumors. Early French writers (Mallassez and Monod, Carnot and Marie, Dopter) believed they were sarcomatous and attributed vaso-formative properties to them. A similar view has also been expressed more recently by Sternberg, who thinks the multinucleated masses in the tumors are endothelial and that the coincidence of these "endothelial sarcomata" with teratomatous tissue is merely accidental. But this view has not been generally accepted.

Mönckeberg concluded that the elements resembling syncytial masses found in these tumors are not always the same, and divided the tumors into two groups: (1) those with chorio-ectodermal formations and syncytial epithelium—and to these he would add teratoid tumors in which the syncytium is similar but not of epithelial origin; (2) simple or teratoid tumors with perivascular lymphangio-endotheliomatous formations and syncytial protoplasmic masses with an endothelial origin. Conforti also thinks this tumor is neither ectodermal in origin nor related to teratomata, but that it is derived from capillary vessels and, therefore, a perithelioma. According to this writer, the multinucleated masses are giant cells formed in response to a chemical stimulus from the necrotic tissue of the tumor, and are similar to the giant cells formed around a foreign body.

Most writers, however, have considered that the portions of these growths which resemble chorio-epitheliomata are epithelial, although their views differ regarding the nature and origin of the tissue resembling trophoblast. A majority of the observers agree that the tumors should be considered teratomatous with actively proliferating malignant portions indistinguishable from true chorio-epitheliomatous tumors.

In general, therefore, the theories of origin of teratoma have been utilized to explain the genesis of these tumors, but



the nature of the malignant chorio-epitheliomatous tumor has been the subject of a number of hypotheses. The views expressed have chiefly dealt with the question of "specificity," *i. e.*, the question of identity of these tumors in men and of morphologically similar tumors in women. Schlagenhauser, taking the view that teratomata originated from a fertilized polar body, advanced the hypothesis that chorio-epithelioma of the testicle arose from elements in the fetal membranes formed during the development of the tumor. He believed that its genesis is quite analagous to chorio-epithelioma in the female, and that it arises from specific chorionic epithelium. This opinion is based chiefly upon the re-examination of a case reported by Breuss which Schlagenhauser interpreted as an hydatidiform mole. Such a degeneration, Schlagenhauser affirmed, was known to occur only in tissue of trophoblastic origin and its presence indicated a similar origin for these tumors. Nevertheless, he has failed to convince others that the tumor in question was really an hydatidiform mole; and his view that these testicular tumors arise from a fertilized polar body is an hypothesis which has not found wide support.

Most writers hold that chorio-epithelioma of the testicle originates from a dislocated blastomere and likewise the same theory at present has a considerable vogue in explaining the origin of teratoma. During the early stages of segmentation of the ovum, displaced cells are supposed to lodge in the *Anlage* that forms the testicle and sooner or later begin to proliferate. However, it is not clear that such cells could form trophoblast, and Risel suggests that this phenomenon depends on the metaplasia of certain elements in the teratoma. He believes that the chorio-epitheliomatous tissue is merely a special form of embryonal epithelium arising from the epiblast and does not differ in its origin from other epithelial tissues. This view is based on a case in which a direct transition from definite neuro-epithelial cells of the teratoma to chorio-epitheliomatous masses was observed. In a case of ovarian chorio-epithelioma Pick has demonstrated a similar transition from neuro-epithelium to chorio-epitheliomatous cells, and regards his finding as a proof that an *Anlage* of fetal membranes is not necessary for the formation of the tumor.

On account of the teratomatous tissue found in the metastases a case reported by Steinert is of unusual interest. To account for this finding Steinert mentions three possibilities; (1) Multiple blastomeres deposited in the various organs during fetal life; (2) a primary testicular tumor composed of many blastomeres some of which later were carried to different organs; and (3) cells transported from the testicular growth which were derived from a misplaced blastomere and which were still at a sufficiently early stage to permit development of all three layers in the secondary tumors.

The origin of chorio-epitheliomata from the interstitial cells of Leydig seems quite improbable, though Nussbaum has stated that these are undeveloped germ cells.

The derivation of chorio-epitheliomata from the spermatogenic cells has received little attention, probably because such

a conception would involve the much disputed question of parthenogenesis. In this connection a rather striking fact brought out by the study of the age of the patients in the reported cases may have some significance. Of the 38 cases in which the ages were given, 3 were under 20 and 5 were over 40, the youngest being 16 and the oldest 45 years of age; 16 cases occurred in the 3d decade, and 14 in the 4th. No cases before puberty have been recorded and none after sexual activity ceased. This strongly suggests that the development of the tumor is intimately associated with spermatogenesis. Furthermore, it seems rational to apply to these tumors the theory proposed by Adami to explain the origin of ovarian and testicular teratomata. This modified parthenogenic or germ-cell theory attributes the tumors to aberrant development of the spermatogonia or oogonia (or possibly their precursors) but not to the spermatozoa or ova themselves. It is known that certain cells—the germinal blastomeres, recognizable at an early stage of segmentation—are set apart and eventually carried to the generative glands where they later form ova or spermatozoa. All the intermediate stages of development between the primordial germinal blastomeres and the ova and spermatozoa retain the totipotential characteristics necessary for the formation of the three germinal layers of an embryo or an embryoma. Consequently a derivative from a germinal blastomere, normally present in the testicle, may take on aberrant characteristics and form a teratomatous or terablastomatous tumor, containing elements of fetal membranes. This hypothesis seems to meet all requirements.

It has been shown by Beard and other zoologists, who have followed the germinal blastomeres from the earliest stages of development, that certain of them may be dislocated and become included in other organs, for example, in the cranium, the gill-clefts or abdominal and thoracic cavities. From such dislocated cells may have arisen the chorio-epitheliomatous tumors described in the mediastinum by Ritchie and Frank, that in the omentum by Bonney and also in the cases noted by Boestrom and by M. Askanazy in which the original tumor was found in the brain. Similar growths originating in the ovary have been described by Lubarsch, Kleinhaus, Pick, Glinski, and Michel. Such an origin from a derivative of a germinal blastomere would explain the great predominance of the primary growths in the generative glands and it is noteworthy that the tumors have constantly developed during the period of active proliferation of the spermatogenic elements. Furthermore, it is of interest that Loeb, in the examination of the ovaries of 484 guinea-pigs, found structures resembling chorio-epithelioma 23 times. These were transitory tumors which were later converted into fibrous tissue. The growths were circumscribed and metastases were never formed. He attributed their origin to the parthenogenic development of ova, which developed only placental chorio-epitheliomatous tissue because of contact with the tissues of the host.

Indeed it is difficult to believe that the chorio-epitheliomatous portions of testicular tumors are not identical with the trophoblastic growths in the uterus. Morphologically the



two tumors are indistinguishable; they are of equal malignancy, they metastasize in a similar manner, both have a marked vaso-destructive action and both contain glycogen.

The recent demonstration by Abderhalden of a specific ferment (?) in the blood-serum of pregnant women may be of value in elucidating the disputed question of the specificity of these testicular tumors. When mixed with placental tissue, this ferment-like body in the serum has the property of liberating substances which give a test for amino-acids. If it should be found that the serum of patients with chorio-epithelioma of the testicle contains a similar substance acting upon placental tissue, this fact would strongly support the view that chorio-epithelioma of the testicle is a "specific" tumor and that it is genetically equivalent to chorio-epithelioma in women. Certainly this test should be made on the serum of all patients with these tumors. However, it must be remembered that a negative test would not exclude their trophoblastic origin. The commonly accepted view regarding these substances in the blood of pregnant women is that they are part of a protective mechanism against the spread of trophoblastic tissue. And, since cases of chorio-epithelioma show very little immunity against this tissue, the serum may possibly give a negative reaction.

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# MITHRIDATIUM AND THERIAC, THE MOST FAMOUS REMEDIES OF OLD MEDICINE.<sup>1</sup>

By GEORGE W. CORNER, M. D.,

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Of all the nations which at one time or another came to mortal conflict with Rome, none is now more utterly forgotten than the kingdom of Pontus. Her landmarks are uprooted, her temples are fallen, and of her mightiest ruler there remain but distorted legends. Mithridates the Sixth, surnamed Eupator, was the King Alfred of his day; or perhaps was more like Peter the Great, to whom Reinach the historian compares him. Between war and turmoil he found time to encourage at his capital all the arts and sciences. He spoke two and twenty languages, and conversed with subjects from all parts of his realm without need of interpreters. To him the famous Bithynian physician Asclepiades dedicated his works, and he himself dabbled in medical studies. It is certain that he was an enthusiastic experimenter with deadly poisons, and it is likely that his researches extended to the dosing of prisoners with fatal drugs. Tradition says that he carried out surgical operations upon his courtiers, and even poisoned some of his own family through excess of scientific zeal. Ever fearing treacherous attacks upon his life, and confident of his medical knowledge, he undertook to accustom his own body to harmful drugs by taking small daily doses of all sorts of poisons, both animal and vegetable, and finally compounded that strange pharmaceutical medley called after him Mithridatium, whose amazing history is briefly traced in this paper.

The story of Mithridates' death in the year 63 B. C. fires the imagination even at this day, and calls up lurid visions of Oriental strife. Routed at last by Lucullus and Pompey, the king escaped with two daughters (the queens of Egypt and Cyprus) and a few faithful followers to his castle at Pantikapaion on the Bosphorus, where he was besieged by his unfaithful son Pharnakes. His citadel in ruins and capture imminent, Mithridates drew from his jewelled sword-hilt a vial of poison and shared it with his daughters. The women expired at once, but the king, by a strange ironical fate, having hardened his body against poisons, was unharmed by the potion. Then, as the Roman soldiers burst into the palace, the king gave his last command, and fell upon the drawn sword of the last remaining member of his bodyguard.

Pompey had such superstitious regard for the memory of his enemy, that when a coffer was found in the citadel, full of manuscripts in the king's hand, recording his researches, the papers of the royal poisoner were given to the freedman Linaeus to be translated. Thus the formula and composition of the Mithridatium were preserved, to be revered as a potent remedy for 1900 years. The works of Linaeus were, of course, extant in the time of Pliny the Elder, who quotes from him a simple recipe for the drug: "Two dry walnuts,

20 leaves of rue, two figs, pounded and strewn with a little salt; taken fasting in the morning it should protect against every sort of poison during the day."

Whether or not this was the original composition of Mithridates, by the first century A. D. another and more complicated prescription was honored with his name. It was preserved in verse by Damocrates, an obscure physician, and is quoted in Galen's *De Antidotis* in a Latin poem of 30 verses.

The prescription is also given by Celsus (Lib. I, Cap. xxiii). But we do not have to search dusty pages of the ancients, for the same concoction extolled by Celsus and Galen in the first and second centuries is published with commendation in the English dispensatories of the eighteenth century.<sup>2</sup>

To decipher the nature of the ingredients, however, is a task of another sort. Different authors and editions give varying prescriptions, but the oldest existing formula is that of Celsus, which contains 33 ingredients, the nature of some of which we can only guess.

The chief of Nero's medical attendants was Andromachus the Elder, a man notable for skill in healing, upon whom first of Roman court physicians was bestowed the honorable title of Archiater. By this time the Mithridatium had come to hold a regular place in the doctor's armamentarium and perhaps it is not unduly fanciful to imagine the bloated features of Claudius Nero himself twisted awry over a nauseating dose of it. Andromachus undertook to improve the formula by adding new substances and, in order to protect his successors from error in compounding, put his prescription into 175 Greek iambic verses.

In the poem the physician dedicates his remedy to his sovereign, recommending it against poisons, serpent-bites, and the graver diseases, including blindness, incipient phthisis, dropsy, stricture, rabies, and so on. He then gives the formula and dosage. The additions made by Andromachus consist chiefly of squills, viper's flesh, and opium in generous quantities; he, too, mixed the ingredients in honey to make the drug more agreeable. The name *theriaca* is from the Greek word signifying wild or venomous beast, in token of the curative power of the medicine against the bites of animals. This is the prescription which held supreme honor as an antidote against all poisons, and as a remedy in all febrile diseases, until 1750 A. D. Under the name of Theriaca Andromachi, or Venice treacle, it is to be found in every work on the treatment of fevers for 1800 years.

What pharmacological conceptions led to the use of such mixtures is difficult to imagine. Most of the ingredients belong to those classes called by Paulus Aegineta desiccative

<sup>1</sup> Read before The Johns Hopkins Hospital Historical Club, January 11, 1915.

<sup>2</sup> See various editions of the London and Quincey's Dispensatories.



and heating, and should thus be useful against the supposedly cooling action of poisons and the acute infections. Many mediæval writers report that overdoses of theriac produce undue sweating and prostration. It is unnecessary to explain the addition of opium. The use of viper's-flesh forms a most interesting chapter of ancient medicine. Perhaps a clue to the old theories which led to its use is found in the *Royal Pharmacopœia* of Moses Charras (1678):

The powder of vipers is very much enlivened with the volatile salt wherewith the vipers abound, which enables it to force its virtues through the pores, though never so close shut, to the more remote parts of the body.

The viper's-flesh is, therefore, apparently the dynamic part of the composition, calculated to help the other ingredients permeate the body. In brief, the theriac of Andromachus was an opiated sudorific, a sort of glorified Dover's powder.

Both the Mithridatium and theriac found favor with Galen, who discourses of them extensively in his *De Antidotis*. In another treatise (*Galenus de theriaca ad Pisonem*) we are told that the noble Marcus Aurelius partook daily of the Mithridatium. Undoubtedly the great popularity and enduring fame of the two royal remedies, during all the Middle Ages, were largely due to the magical influence of the Father of Roman Medicine. No one remembered, or all ignored, the scornful words of Pliny (*Historia naturalis*, Lib. XXIX, Cap. 8):

The Mithridatic antidote is composed of four and fifty ingredients, none of which is used in exactly the same way, and the quantity prescribed is in some cases so small as the sixtieth part of one denarius! Which of the gods, pray, could have instructed man in such trickery as this, a height to which the mere subtlety of human invention could surely never have reached? It clearly must emanate from a vain ostentation of scientific skill, and must be set down as a monstrous system of puffing of the medical art.

The Saracen physicians, unlike their confrères the mathematicians and chemists, made little progress in learning. The shadow of Galen lay athwart the age, and the Moslems mistook it for a great light.

Under these circumstances it is natural that the theriac should be admired by the Arabians, and that in the interminable commentaries upon the Greek and Roman writings, which took the place of original work with them, they should discant at length upon its preparation and uses. Averrhoes and Haly Abbas discuss it, and most interesting of all is a passage from Serapion the younger (ca. 900 A. D.) who describes the following methods of trying whether the theriac be good: First, give of it to the amount of a drachm to a person who has taken a powerful emetic or cathartic, such as scammony or hellebore, and if it counteract the effect of the medicine that has been taken, we know that it is genuine. Second, as Galen directs, having got a wild cock, allow it to be stung by a venomous reptile, and then give it a proper dose of the theriac. If the fowl escape unhurt, we are sure that the medicine is good; but if he die we know that it is not to be depended upon. Third, give a poisonous substance, such as opium, to a cock or dog, and then administer the theriac,

the powers of which may be judged of from the result. Here we have a series of biological tests as scientific as some of those used in modern serum laboratories.

The treacle of Andromachus followed the Crescent even to Cairo and India, whence we shall hear of it later. In the Moslem universities of Spain it was of course taught to physicians, and hence took hold in Europe, for when the Moors were expelled by Ferdinand and Isabella they left behind their scholarly traditions and their Arabic manuscripts, so that a little beacon was left burning in that "windy night of time." There are a dozen extant theses and treatises from all the European countries, touching upon the virtue of the drug, especially in the plague; and as I have said, the theriac is recommended in every book on fevers and poisons until nearly 1800. Thus Daniel Defoe, in *A Journal of the Plague Year*, quoting his "particular friend, Dr. Heath":

"Only that," says he, "some recommend one thing as most sovereign, and some another. Some," says he, "think that *pill ruff*, which is called itself the antipestilential pill, is the best preparation that can be made; others think that Venice treacle is sufficient of itself to resist the contagion; and I," says he, "think as both these think, viz., that the first is good to take beforehand to prevent it, and the last, if touched, to expel it." According to this opinion, I several times took Venice treacle, and a sound sweat upon it, and thought myself as well fortified against the infection as any one could be fortified by the power of physic.

The remedy was indeed so famous that its name became in several languages a general term denoting any antidote. So the Man of Lawe's comparison:

Christ, that which is to every harm triacle.

And Chaucer tells us, too, that a store of the remedy was in demand upon the immortal pilgrimage:

Seyde I nat wel? I cannot speke in terme;  
But wel I woot, thou dost my herte to erme,  
That I almost have caught a cardiacle.  
By Corpus bones! But I have triacle,  
Or elles a draught of moyste and corny ale  
Or but I here anon a merry tale,  
Myn herte is lost for pitee of this mayde.

(Words of the Host to the Physician.)

Some sub-editions of the "Bishops' English Bible of 1568 are called by bibliographers the "Treacle Bible," on account of their rendition of the very familiar verse, Jeremiah viii, 22: "Is there no *tryacle* in Gilead? Is there no physician there?" (The Douai Bible has the same verse less poetically, thus: "Is there no *rosin* in Gilead?")

A few men raised feeble voices against the theriac during all these centuries. Three of them get a hearty scolding from Diemerbroeck:

Capivaccius, Trincavellius, and Julius Alexandrinus alone are silent, and try to exterminate from medical practice this divinest and most useful of drugs.

Trincavellius seems also to have held the heretical opinion that the plague was a hot disease and not to be treated with sweats and calorifics. Besides these three culprits, one Vincentius Calzavelius, a physician of Brix in Bohemia, wrote in



1570 a thesis *De theriacae abusu in febribus pestilentibus* upholding the same view. So far as I know, these were the only medical men who opposed the use of the drug, and the two of them, whose works I have examined, opposed it in the pestilential diseases only, not objecting to its use in other ailments. Robert Burton, the anatomist of melancholy, has a polemic against treacle and all other compound prescriptions, but then he was no physician, but a clergyman, and as he says himself, like a ranging spaniel barked at every bird he saw.

The drug could not only be used directly, but was often made an ingredient of other prescriptions, and was put into powders, electuaries, potions, waters, pills, ointments, and plasters. There were several grades of theriac in commerce, according to the place of manufacture, as that of Paris, of London, of Venice, and so on. Since Venice, with its great fleet, had the most direct trade with the Mediterranean lands whence most of the ingredients came, its product was considered the best. From this fact the medicine was called by the name commonest in English books, Venice treacle. Then there were modifications of the formula, such as those of Monavius the German, of Edinburgh, and others. There is an apt passage in Burton's *Anatomy of Melancholy*:

Mellichius, Cordus, Wecker, Quercetan, Renodeus, the Venetian, Florentine states have their several Receipts and Magistrals: They of Noremberge have theirs, and Augustana Pharmacopœia, peculiar medicines to the meridian of the City: London has, every City, town, almost every private man hath his own mixtures, compositions, receipts, magistrals, precepts, as if he scorned antiquity and all others in respect of himself. But each man must correct and alter to shew his skill, every opinionative fellow must maintain his own paradox, be what it will; *Deliriant reges, plectuntur Achivi*: they dote, and in the meantime the poor patients pay for the new experiments, the Commonalty rue it.

There was a disagreement between the Colleges of London and Edinburgh as to the manner of preparing the viper's-flesh<sup>3</sup> which was used in making the theriac, London apparently preferring the imported article in the form of troches, whereas the wise men of Edinburgh held that a fresher and therefore better product could be made from native vipers.

A learned discussion on "Troches of Vipers for the Theriac" ends thus:

Take of Viper's-flesh after the skin is stripped off, the fat and entrails being taken out, 8 ounces; of the finest wheaten Bread, or rather Bisket, powdered and sifted, 2 ounces. Let them be formed into little Troches, by anointing the hands with Opobalsam, or Oil of Nutmegs by expression; then dry them upon the bottom of a sieve inverted in some open place, where the air hath passage through; and turn them often till they are thoroughly dry. . . . Vipers are frequently brought to us from several parts of Italy, and particularly from Venice, but they that lay most stress upon them, chuse rather to be the preparers themselves with our own Vipers here; which at the proper time of year are full as good, and the Troches are much the better for being fresh; which they cannot so well be when they come from abroad. The College of Edinburgh prefer the dried Viper's-flesh to the Troches thereof.

The formulæ varied so much by this time that Johann Nolt of Lübeck thought it worth while to print a large table giving

in parallel columns 11 formulæ for Andromachus' theriac, for purposes of comparison. The Orviétan celebrated by Molière<sup>4</sup>

O grande puissance  
De l'orviétan!

was one of the complicated mixtures based upon theriac.

One of the most notable theriacs was that of Matthiolus, court physician to the Emperor of Austria about 1550. His prescription contained 127 ingredients, one of which was ordinary theriac, itself containing fifty-odd more substances, to say nothing of a half-dozen other compounds thrown in for good luck. Diemerbroeck calls it

famosa illa antidotus, magna illa congeries plurimorum simplicium sine ordine, sine methodo, sine ulla ratione simul congestorum ac conjunctorum.

This masterpiece reigned as the king of drugs until Joseph Duchesne, (Latinized *Quercetanus*) invented and published in 1607 a theriac so surpassing in its powers that he called it *Benedicta*, the blessed. Not even content with such a blessing, Frederic Greif, of Tübingen, took in hand the Blessed Treacle, boiled it down to the consistence of a pill-mass and added various substances until he evolved a prescription of 150 ingredients, and so mighty in its virtues that it was called the Exalted or Celestial Treacle.<sup>5</sup>

It must be remembered that the therapeutists of that time did not desire drugs to meet single indicated symptoms, as in modern medicine, but just as the alchemists were searching for the universal element, so the pharmacists were ever seeking a universal remedy, wishing to place beside the Philosopher's Stone an equally magical Physician's Stone, potent to assuage all disordered humors, to charm away all ailments at a single stroke, and valuable in every diverse condition. Christianus Paullinus (1643-1712) published a treatise on the Celestial Theriac, giving an index of lesions curable therewith, which covers the entire catalogue of diseases, including "all the external and internal malignancies" from nightmare through toothache and "obstruction of the spleen" to scabies.

Of course these medicines, composed of such numerous ingredients, most of them exotic and many rare, were very expensive and to be had only by the rich. Therefore, there was a cheap kind, the *theriaca diatessaron*, made for the poor, having only five ingredients (gentian, laurel-berries, birthwort, juniper-berries and honey) but in spite of its simplicity, "excellent against fevers and poisons." I like to fancy that the sulphur and molasses, "spring medicine" of our great-grandmothers, was a poor relation of the celestial sulphur-and-honey of Tübingen.

The fame of theriac was so great that the drug passed out of the hands of legitimate physicians, and became an article of commerce among the people. To that rascally mediæval army of peripatetic mountebanks, palmers, mendicant friars and pardoners, was added a troop of *triacleurs*, who wandered from place to place selling their nostrum to the rustics. Bern-

<sup>4</sup> L'amour medecin, Act II.

<sup>5</sup> Vide Rosa, *De theriaca coelesti*, 1703.

<sup>3</sup> See Quincey's Dispensatory, London, 1749.



hard, in his little volume about theriac in France, quotes the title of an old farce, "Le Pardonneur, le Triacleur, et la Tavernière," and prints a magistrate's license of the sixteenth century, allowing a friar and a triacleur to travel in company; a convenient arrangement which permitted a layman to buy pardon for his sins and balm for his diseases from the same firm. Needless to say there were many tricks of the trade and plenty of fraud in the treacle business.

"I remember," says Matthiolus, "seeing one of these fellows who gave his boy 'poison' substituted in this sleight-of-hand way, and then pretended he would not give medical aid until the boy's pulse ceased and he was at the brink of death, in order to prove the power of his false and adulterated theriac. Having first admonished the sly youth to repress his respiration, to change color, to roll his eyes, and to contort his face, the demonstrator called to his side a physician who was among the bystanders (not a very shrewd man, to my way of thinking) and requested him to testify publicly that the boy's pulse had ceased. The good doctor, so thoughtlessly made the dupe of the peddler, announced to all that he found no pulse in the boy; which he might well say, since the fellow knew how to stop his pulse, as Galen describes, Lib. 6 *de placitis Hippocratis*, where he says 'arteries, like nerves, if cut or compressed, are deprived of all pulse and vibration.' They had contrived to put a cord about the boy's upper arm. . . . After that young scalawag had taken the quack's medicine, he gradually worked the cord loose and finally returned to a natural condition."

The tricks and frauds of such villians as these were taken as a great insult by decent physicians like Matthiolus, and by honest apothecaries. In self-defense, therefore, in the seventeenth century the regular profession began to hedge about the preparation and sale of theriac with divers laws and customs tending toward uniformity. The drug was often compounded in the public presence by reputable men, in order that the populace might know that everything was done in proper manner. The first of these public confections of theriac was held at Montpellier in 1606 by Maître Catalan, chief apothecary of the city. He set a fashion, which was thereafter continued, of publishing a book in Latin, containing a discussion of the history and nature of the drug, together with certificates from the authorities that due care had been taken in the work. The best-known man connected with such performances was Thomas Bartholin, the Danish anatomist, who made theriac in 1671. He had a certificate from the faculty at Padua that the pastilles of Italian vipers they had sent him were freshly and skillfully prepared.

About this time there began to be sumptuary laws or at least regulations of the apothecaries' guilds, forbidding apothecaries to make the drug without permission.

At Paris, the public preparation of theriac took a very elaborate form. We learn from M. Planchon that Moses Charras, "The King's Chief Operator in His Royal Garden of Plants," was the first to make it publicly at Paris (1670). The participation of Charras would undoubtedly lend dignity to the affair, since he was a man of note and author of the *Royal Pharmacopœia* which I have already quoted, a work which was translated into many languages, even into Chinese. A little later the official preparations were held by the Com-

pagnie des Marchands Apothicaires, who yielded their privilege in turn to a Société de la Thériaque open to master-apothecaries, with a large capital and full authority to compound the remedy. Apparently the last public preparation was made in 1790.

These solemn ceremonies lasted from 15 to 17 days, beginning at 5 A. M. The session was opened by the presidents of the college of apothecaries and the faculty of medicine, the lieutenant-general of police and the king's procurator. The person to whom had been given the honor of making the theriac addressed the audience, lauding the virtues of the drug, usually with many quotations from the ancients and much show of oratory. He then gave a scientific description of the ingredients, exhibited them to the public gaze, and finally weighed and mixed them. The finished product was stored in a porcelain jar 88 centimeters high, (still extant in Paris) which was locked with three locks, the keys of which were held by three officials high in the councils of the apothecaries. Several times during the fortnight of preparation there were addresses and collations.

It is easy to see the psychological and financial advantages of such pomp and circumstance. Imagine the effect of a public preparation of Peruna on Mount Vernon Place in Baltimore, with addresses by the mayor and the state chemist, the medical faculties attending in academic robes, assisted by Sousa's band!

It is astonishing that this pedantic fol-de-rol went on without a word of protest for so many years. But a bold opponent was lying in wait—no less a person than William Heberden, he of "Heberden's nodes." In his "*Antitheriaca—An Essay on Mithridatium and Theriaca*," a little volume published in 1745, he makes a caustic attack upon Venice treacle, so level-headed and withal so learned, that I wish time permitted to read the whole 19 pages. Let the following suffice here:

MITHRIDATES, the famous King of Pontus, had a strange affectation of superior skill in the powers of Simples. His Courtiers, we may imagine, flattered him upon it, and he has accordingly been delivered down to us as a second Solomon. Whereas if we consider the little leisure that he had for his own inquiries into this part of nature, or the little helps that he could have from the people about him, we must conclude that his knowledge was very inconsiderable. However, Pompey seems to have been possessed with the vulgar opinion and, after he had conquered this King, took uncommon care to secure his writings, in hopes of some mighty treasures of natural knowledge. He was soon convinced of what he might easily have foreseen, and is represented as laughing at the disappointment of his own credulity, when instead of those great arcana, he found only one or two trifling receipts.

There were probably some artful people at this time, who were not disposed to part so easily with the great expectations that had been raised, nor to lose this fair opportunity of enriching themselves by a plausible imposture; which has since been several times repeated and is frequently practiced among us at this day. For soon after, there was published in Rome a most pompous medicine with the name of *Antidotum Mithridatium*, which was pretended to have been found among his papers: though Plutarch, who gives a minute detail of them (mentioning the Love-letters and several interpretations of Dreams), says not one word of this famous medicine; which one can hardly think that he would



have omitted if he had found the tradition supported by any proper testimonies. The authority of Q. Serenus Samonicus is more positive, who says that, notwithstanding the many receipts of *Mithridatium* that were handed about, the true medicine found in the cabinet of Mithridates was only that trivial one consisting of 20 leaves of rue, two dried figs, one grain of salt, and one nut. So that there is some reason to suspect that Mithridates was as much a stranger to his own antidote as several eminent physicians have since been to the medicines that are daily advertised under their names.

And so on, with many quotations from erudite works of all ages, for Heberden will fight with authority, he says, that which is defended by authority. He points out that one of the great reasons for the popularity of treacle was the mediæval fear of murder by poison, which led people to make much use of antidotes. But the only poisons known when the treacle was composed were hemlock, aconite, and the venoms of beasts. How then could the drug be of use against the newer poisons, such as arsenic, quicksilver, and the like? Moreover; first, the formula has never been the same for a hundred years together; second, there is grave danger of error and overdosing when opium is given in such complicated mixtures; third, to give theriac is to load a sick man's stomach with useless things; fourth, whatever effect the theriac has can be gained with a few simple drugs.

Allow me to quote one more paragraph, that in which he comes to a brave conclusion:

It still goes on to be prepared in the old manner, as near as may be, in all the great cities of Europe. Its power indeed and fame has of late been manifestly declining; and we may hope that its reign will not last much longer. Enough has surely been given to antiquity: let not length of time, which has ever been the fatal enemy of falsehood and imposture, be made in this instance to support and protect them. Perhaps the glory of its first expulsion from a public Dispensatory was reserved to these times and to the English Nation; in which all parts of Philosophy have been so much assisted in asserting their freedom from antient fable and superstition; and whose College of Physicians in particular hath deservedly had the first reputation in their Profession. Among the many eminent services, which the authority of this learned and judicious body hath done to the practice of Physic, it might not be the least that it had driven out this medley of discordant Simples, which, perhaps, has no better claim

to the title of *Mithridatium*, than as it so well resembles the numerous, undisciplined forces of a barbarous King, made up of a dissonant crowd collected from different countries, mighty in appearance, but in reality an indifferent multitude, that only hinder one another.

Heberden promptly followed up his words by deeds, and forced a vote in the College of Physicians, on the expulsion of theriac and Mithridatium from the London Pharmacopœia. It is said that when the ballot was taken there were 13 votes in favor of retaining the theriac, 14 against it. Thus came to an ignominious defeat, in an English committee-room, after a glorious career of 2000 years, the greatest medicine of all the world.

Although Heberden had dealt the death-blow, the theriac was to linger on a while in many parts of the earth. Alexander Monro, Senior, cured himself of a bad angina by its use, as late as 1781; and Benjamin Bell says that in his time it was in frequent use in England as an application to ulcers.

In 1835, Dr. Malcolmson of Madras was told by some of his native patients of a drug which had worked wonderful cures in beri-beri called Teriak Farook. He was able to purchase some of it in India, finding it in cannisters bearing Turkish characters stating that it was invented by a famous Turkish doctor called Andromakoo, in the fortified city of Vendeck. He found, however, on pulling off the outer label, another showing that the material really came from Venice; it represented, therefore, the last trace of that once-mighty commerce of Venice with the East. The word *farook*, applied to the drug, is explained by a passage in Prosper Alpinus,<sup>6</sup> who states that in his time theriac was in much use by the Sultan at Cairo, and was called *Tharach faroch*, as Mahomet called his successor Omar faroch, the unsurpassed. In 1837 Maxwell of Calcutta read Malcolmson's article, found some theriac in the bazaars, and tried it on himself and many beri-beri patients without result.<sup>7</sup> This is the last recorded use of theriac, in the realm and reign of Queen Victoria the Good, 1899 years after the death of Mithridates.

<sup>6</sup> *De medicina Aegyptiorum*, 1591.

<sup>7</sup> *Indian Jour. Med. and Phys. Soc.*, 1837.

## IS PATHOLOGIC METABOLISM IN THE PARENTAL ORGANISM RESPONSIBLE FOR DEFECTIVE AND MONSTROUS DEVELOPMENT OF THE OFFSPRING? \*

By E. I. WERBER, PH. D.

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One of the most interesting and most difficult problems of pathology as well as of general biology is that of the causes underlying defective, atypical development. Leaving out of consideration the "explanation" which was given by superstition, and which was generally accepted until in recent times

it had to retreat before scientific investigation, we find, besides crude theories of mechanical interference with the developing embryo, mainly two theories which seem to offer a reasonable explanation.

A very significant suggestion has recently been made by F. P. Mall<sup>1</sup> in his monograph on the causes underlying the origin of human monsters. He states that a careful study

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of a collection of 163 pathological embryos has led him to assume that the defective development of these embryos was due to a condition which he terms "faulty implantation" of the ovum in the wall of the uterus. According to his view, which seems to be well supported by clinical data, this defective implantation is due to a diseased condition of the uterus. The imperfect implantation of the ovum in the uterus would, he concludes, make its adequate nutrition impossible, thus bringing about defective development and eventually leading to the embryo's early death from inanition. According to this theory, therefore, which seems to go far towards accounting for monstrosities in embryos aborted during the first two months of pregnancy, a healthy ovum may give rise to a monster when discharged into a diseased uterus where it fails to become properly implanted.

Another important hypothesis was advanced by O. Hertwig<sup>2</sup> in 1896. Concluding from his experiments in which he could produce spina bifida in amphibian embryos by subjecting the fertilized eggs to the action of 0.6 per cent to 0.7 per cent solutions of sodium chloride, Hertwig suggests that the formation of monsters in human beings may possibly be due to the presence of certain poisons, such as alcohol, or toxins in the blood of the mother. This seems to be a very valuable hypothesis, and had it attracted the attention which it justly deserves, we might by this time be able to answer many a question in teratology and possibly also in general medicine, which thus far has eluded attempts at inquiry.

Hertwig's suggestion seems to find ample support from discoveries which have been made in recent years. For experimental teratology has shown us that there are various physical as well as chemical means by which the development of the ovum can be caused to deviate from the norm or even to become monstrous. And the recent researches of Féré,<sup>3</sup> Stockard<sup>4</sup> and McClendon,<sup>5</sup> who obtained one-eyed monsters by submitting developing eggs to the action of such injurious substances as magnesium chloride, alcohol, ether, alkaloids, etc., would seem to indicate that the monsters found in nature may also be due to the effects of chemical agents.

With this in mind, in the summer of 1911, I performed a number of experiments on the eggs of the marine teleost fish *Fundulus heteroclitus*. Thinking that the monsters found in nature might possibly be due to an excessive retention of nitrogenous waste compounds in the blood of the mother during pregnancy, I submitted the fertilized eggs in very early cleavage stages to the action of solutions of sodium nitrate and potassium nitrite in sea-water. Although in these experiments I did obtain cyclopean monsters in both nitrate and nitrite solutions, the percentage of the eggs developing in this manner was so low that the results could not be considered as conclusive. Possibly more experimentation is needed in order to obtain more definite results with these chemicals, but I have never repeated them again, thinking that the substances which are found in the urine of individuals afflicted with certain diseases of metabolism may be more toxic and thus more likely to cause pathologic development of the

embryo in the uterus of a mother whose metabolism has been seriously impaired.

As a preliminary test of this hypothesis, I carried on during the past summer some experiments on the fertilized eggs of *Fundulus heteroclitus*. The eggs were submitted in early cleavage stages (2 to 4 or 4 to 8 and 8 to 16 cells, respectively) to the action of solutions of a number of toxic substances known to be found in the urine of persons suffering from disturbances of metabolism. Only two substances, butyric acid and acetone, have so far given me definite results.

When fertilized fundulus eggs were exposed to the action of a 1/12 to 1/14 gram-molecular solution of butyric acid in sea-water for about 15 to 20 hours and then transferred to sea-water, a very large number of them gave rise to monsters. This was also found to be the case in solutions of acetone. Here the eggs were exposed in a number of dishes to the action of solutions of 20, 25, 30, 35, 40, 45 and 50 cc. of a gram-molecular solution of acetone added to 50 cc. of sea-water. A varying number of monsters were found in all dishes, the relative number of them increasing with the strength of the solution up to 40 cc. of acetone, and decreasing in solutions still stronger, which caused the death-rate of the eggs to increase. The results obtained in both series of experiments, with butyric acid and acetone, being very much alike, it will not be necessary to enumerate separately the deformities produced by each.

Cyclopia, asymmetric monophthalmia and mikrophthalmia were found to occur very abundantly. Several cases of asymmetric monophthalmia were found which differed from others of this category, in that an apparently free eye had developed on the yolk-sac at a considerable distance from the embryo. Probably the most striking of the results obtained in this investigation were seen in certain eggs in which could be observed a solitary eye, while nothing else could be seen to indicate the presence of even a deformed embryo. It is difficult to know just what may have happened to that part of the germ-disc which was to form the rest of the embryo. Such cases as this, and others which were obtained by experimentation, confront us with one of the most difficult problems of biology, because they obviously elude all attempts of interpretation, the sequence of events being obscured. Practically all other known deformities of the eye, such as coloboma, total blindness, or presence of lenses only, or presence of supernumerary lenses, were frequently found. Great numbers of eggs developed into anterior half-embryos similar to those which were first obtained experimentally by Roux<sup>6</sup> in the frog. These hemiembryos nearly all exhibit high degrees of malformation, but in some of them a functioning though rudimentary heart could be observed.

Many embryos exhibited defects of the ear-vesicles, which had swollen up to an unusually large size. Others were apparently hydrocephalic, their heads being enormously enlarged. In some embryos large oedematous swellings were also found in other parts of the body.

Various deformities of the heart and blood-vessels were



found in all malformed embryos, except in some cases of median cyclopia. Some possessed no heart at all, while in others it was more or less rudimentary, though usually functioning if present at all. The rate of the heart beat varies with the degree of the abnormality of the organ, and is, as a rule, very sluggish in all monstrous embryos, excepting those in which the only defect superficially noticeable was cyclopia. The range of variation in the development of blood-vessels is also very wide. There may be merely blood-islands scattered on the yolk-sac, rudimentary, imperfectly connected, or in some instances more or less normal vessels.

The tendency of butyric acid and acetone to produce twins seems to be very slight, for I have recorded the occurrence of only a few such cases in my experiments.

It would be far beyond the limits of the present communication to describe, no matter how briefly, all deformities which I observed in these experiments. This will be done in another publication, as soon as a careful microscopic examination of the collected material may permit it. For the present it will suffice to state that an unusually great variety of monsters were found to occur when fundulus eggs were subjected to the action of solutions of butyric acid and acetone. Most of the monsters observed resembled morphologically very much those which have so often been described in human beings.

Other toxic substances, found in pathologic conditions of metabolism, have also been tried, but the results obtained so far have not been conclusive and call for further investigation.

Let us now see what conclusions may be drawn from these experiments. It was shown that butyric acid and acetone have a very injurious effect on the fertilized ovum, causing it to develop in a highly atypical, monstrous manner. The monsters thus produced resemble morphologically those known to occur in nature in the human being and in other mammals. Does this not suggest that the monsters—or at least a great number of them—found in nature may be due to the action of any one of these or other substances in the human body associated with pathological conditions of metabolism? The disturbances of metabolism may vary in degree and the quantity of the toxic substances, which they produce in the body, would vary accordingly. Such variations in the quantity of toxic substances in gravid females may account for the variations in degree of injury exhibited by defective embryos aborted at different periods of gestation or even for some defects found after full-term birth in individuals which may even be apparently normal. I am inclined to think that careful clinical family records may amply justify this assumption.

This hypothesis, that the pathological condition of the embryo or full-term offspring, respectively, may be due to parental pathology, if borne out by positive results of experiments on mammals, may eventually furnish us a secure, scientific basis for the etiology of many congenital defects of the sense organs, the central nervous system (responsible for such conditions as hydrocephalus, epilepsy etc.) and other organs. Some of these defects may pass unnoticed, until the individual is well advanced in life. Furthermore, the effects

of an intra-uterine or possibly even pre-uterine poisoning of the embryo or germ-cell, respectively, may not always manifest themselves morphologically. The influence of very small traces of toxic substances due to the pathologic metabolism of the mother (or possibly even the father?) may be slight enough to cause in the organism only certain chemical, unaccompanied by gross morphological, changes. These chemical changes may lead to what I would term a gradual deterioration of the chemical make-up of the individual, the effects of which may become fatal at some point of his life. It is not even inconceivable that such a deterioration may be inheritable and thus eventually lead to racial degeneration. To this latter assumption I am led by the remarkable results which Stockard<sup>1</sup> obtained by breeding in various combinations animals, whose ancestors had been exposed to very long periods of almost constant intoxication (six days of the week) from the inhalation of alcohol fumes. He finds that the results of matings of apparently normal animals of alcoholic parentage deteriorate in a very marked degree with each consecutive generation. There is a relative increase in the still-born litters, increase of the death-rate of the living young and also an increase of animals with congenital defects of the eyes in the third generation as against the second generation.

I do not doubt but that similar and possibly even more marked effects may eventually be found for the toxic substances of pathologic metabolism as compared with those observed by Stockard in his alcohol experiments. The validity of this assumption may be easily tested by mating mammals in which disturbances of metabolism had previously been experimentally produced, and by breeding their offspring. Should the results bear out the contentions of my hypothesis, we shall then know what agents nature employs in causing development (individual or racial) to deviate from the norm. If monstrous or defective development could thus be controlled experimentally, means might eventually be found by which their occurrence could be checked. In view of what has already been said above, it seems needless to dwell any longer on the medical significance of the problem.

It will be the task of the experimental biologist to determine what mechanism may be involved in the action of the toxic products of metabolism on the developing organism. This, however, may be done best, after a large enough body of facts has been established to warrant some morphological generalizations.

Since only experiments on mammals would, in my opinion, furnish the crucial test of the assumption that defective development is due to intra-uterine or pre-uterine poisoning by metabolic products of the embryo or germ-cell, respectively, I intend very soon to enter upon this work. I am inclined to predict that the results will eventually bear out the hypothesis.

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## MEDICINE IN CHINA.

### REVIEW OF REPORT OF THE CHINA MEDICAL COMMISSION OF THE ROCKEFELLER FOUNDATION, NEW YORK, 1914.

In this report of 113 pages are presented the results of the investigations during 1914 of the commission appointed by the Rockefeller Foundation "to study and report on conditions of public health and medicine in China." The commission, composed of President Judson of the University of Chicago (chairman), Mr. Roger S. Greene, American Consul at Hankow, Dr. Francis W. Peabody of Boston and George B. McKibbin (secretary), spent several months in China and visited 17 medical schools and 97 hospitals in China and Manila. Various universities and secondary schools were also visited and numerous conferences held with medical missionaries, government officials and other persons of influence.

In a discussion of the general health conditions, the report states that in China the death-rate is probably higher than in any other known country. The most destructive and widespread diseases are tuberculosis, hook-worm disease and syphilis. Leprosy also prevails. Small-pox is looked upon by the people as a matter of course. The various activities of a public health service as practised in Western lands are almost unknown and isolation hospitals for contagious diseases hardly exist. On the other hand, as the result of the ravages of the plague in Manchuria in 1910-11, a plague prevention service, with several plague hospitals, has been established, and in Canton, Changsha and Nanking a beginning has been made in organizing public health work. No progress has been made, however, with reference to a central public health department.

The native Chinese practitioner is not subject to legal requirements. Anyone who wishes may announce himself as a physician and practise as he pleases. Diagnosis in the main is based on the pulse; and Chinese treatises indicate no less than 98 different types of pulse. A common method of treatment is that of puncturing the body with a needle. The *materia medica* is mainly one of herbs, but some modern drugs, as quinine, are commonly used. Modern patent medicines have a large sale. The Chinese practitioners, although claiming a knowledge of medicine, admit that they know practically nothing about surgery. This is doubtless due to their ignorance of anatomy. The dissection of the human body is contrary to the ideas of the Chinese relating to the future life and is regarded with peculiar horror. (It was not until November 22, 1913, that autopsies and dissection were officially authorized throughout the republic.)

Some physicians trained in Western medicine are found practising in China, but these, with few exceptions, belong to the mission hospitals and the various treaty ports.

The medical schools are discussed under (1) government and private schools, (2) missionary schools, (3) schools for Chinese women, and (4) non-missionary medical schools under foreign control. The strictly Chinese schools have been laboring under great disadvantages during the past four years, on account of disturbed political conditions and the strained finances of the government. Government control is still incomplete and the classes, considering the limited funds, are too large. All the Chinese schools are "greatly handicapped by the fact that not one of them has access to a really satisfactory hospital. It is evident that there is no medical school now in China which is adequately equipped and no school which is adequately manned. Some of the schools under foreign control, however, have really high ideals, and the advanced men on other faculties have the right policies in mind."

China has three medical schools for women alone, besides two in which they may be taught with men. These schools, however, are small, poorly equipped and ill-prepared to train competent physicians. Moreover, they are hampered by the inability to get a sufficient number of girls with a proper preliminary education. The commission concludes that for the present such women as are peculiarly fitted for the profession might better be sent abroad for a thorough training.

The non-missionary schools under foreign control are five in number: Japanese in Moukden, German in Tsingtau and Shanghai, French in Canton and English in Hongkong.

The commission found that a study of hospitals in China "resolves itself almost completely into a consideration of the mission hospital. The more important non-missionary hospitals established by foreigners are for the care of foreigners and have no very definite influence on China itself. The hospitals under Chinese control, whether government or private, are with few exceptions, ineffective and they are chiefly of interest as demonstrating how small an impression high-grade Western medicine has as yet made on China."

A point which the report repeatedly emphasizes is the need of more graduate nurses with foreign training. At present there are only 140 foreign nurses in the country and these are distributed in about 100 hospitals. A great need is enough foreign nurses to serve as teachers in the leading training



schools, which, if thus equipped, would be then capable of furnishing Chinese nurses.

The recommendations of the commission may be briefly summarized as follows:

That the Foundation should undertake medical work in China and as far as possible should cooperate with existing missionary institutions.

That medical instruction in which the Foundation is concerned should be on the highest practicable standard, that is, a standard corresponding to the American high school, supplemented by two years of pre-medical work in English, Chinese, physics, chemistry and biology. English should be the language of instruction, supplemented if necessary by explanations in Chinese.

That the time is not yet ripe for the Foundation to assist in the organization of a large work in relation to public health. A useful foundation for such work might, however, be laid by assisting one or more local hospitals.

That it is not advisable at this time to establish an independent institution for research, but that research be encouraged in connection with the medical schools aided by the Foundation.

That the first medical educational work be in Peking in connection with the Union Medical College; that a new school be established in Shanghai and provisions be made for co-operating with existing schools in and near Shanghai in order to unify medical effort in the lower Yangtze Valley; and that assistance be given the Canton Christian College and that the Yale Mission at Changsha be aided in its medical plans.

That two model tuberculosis hospitals be established.

That six fellowships, yielding \$1,000 and necessary traveling expenses, be maintained to enable selected Chinese graduates to study abroad.

That scholarships be established in the schools aided by the Foundation in order to encourage selected young men, with insufficient means, to study medicine. Ten such scholarships are suggested for 1915-16 and ten additional yearly until the total number reaches fifty.

That the development of hospitals be aided by:

(a) Paying the salaries of additional foreign medical men to be assigned to hospitals already established.

(b) Paying the salaries of Chinese doctors who will work in the hospitals under foreign doctors for considerable periods of time and thus secure adequate practical training.

(c) Supporting a considerable number of foreign nurses.

(d) Increasing the equipment of certain hospitals and more particularly those in connection with medical schools.

(e) Providing in some hospitals the salary for a business manager.

(f) Establishing central diagnostic laboratories in Peking and Shanghai.

(g) Establishing at least one, probably two, extensive libraries of current medical literature.

That the training of nurses be aided by:

(a) Providing dormitories in special cases in connection with schools for nurses.

(b) Establishing scholarships (not over five at first) to enable Chinese women to receive training in the United States.

(c) Translation into Chinese of text-books on nursing.

That from time to time, as may appear expedient, specialists in various branches of medical sciences be sent to China to lecture in medical schools aided by the Foundation.

That provision be made for ten fellowships annually for medical missionaries to enable them to proceed to the United States or Europe for advanced study, and that the annual stipend be \$1,500, with \$1,000 for expenses.

Other recommendations concern a resident commissioner and an advisory committee.

It is at once evident that these recommendations embody a broad plan of medical education which has for its ultimate object a national system of public health administration. Emphasis is laid upon the opinion that to ensure its final success it is essential that a large number of native physicians be thoroughly trained in the methods of Western medicine. Not all the recommendations can be acted upon at once, and that they cannot, the commission apparently fully realizes. However, their adoption as rapidly as may be possible, if approved by the local and national governments, will not only diminish pestilence and its consequences, but will as a result do more than any other single factor in aiding the economic and social progress of the new republic.

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## A CASE OF ABSCESS OF THE LIVER, DUE TO A STREPTOTHRIX.\*

By ARTHUR BLOOMFIELD, M. D.,

AND

STANHOPE BAYNE-JONES, M. D.

The patient, P. K., aged 32, was admitted to the medical service (Gen. No. 98,529), on October 5, 1914, complaining of "stomach trouble." He came to this country from Russia fifteen years ago, and since then has been occupied as a cigarmaker. Four years ago,

however, he went on the road, through the southwestern states, for a year and a half, and then for another year was in the junk business. During the past year he has again been in the cigar factory.

His general health has been good. He is aware of no sores or skin lesions of any sort. There is nothing to suggest a previous

\* From the Medical Clinic of The Johns Hopkins Hospital.



dysentery. Appetite and digestion good. Constipation for the past few years. His teeth have always been bad.

The patient dates his trouble from an upset of the stomach after a dose of salts—about a month before admission (Sept., 1914). Following this there was malaise and fever, his temperature rising to 103° F., with sweats at night. He was said to have typhoid. He had no sharp pain, but his most distressing symptoms were "cramps" in the stomach (epigastrium) and anorexia. He vomited once. There was no cough.

On admission, he said there had not been much change in his condition since onset. He looked pale and sick. The teeth were much decayed; there was pyorrhea. The tonsils were not abnormal. There was no particular glandular enlargement. The lungs showed no marked abnormality in the physical signs except over the right back, where dulness was noted above the angle of the scapula, increasing to flatness at the base. Over this area the respiratory murmur was diminished and the voice was lost. Inspiratory descent of the lung, however, was normal and Litten's sign was present on both sides. The abdomen was at first negative, except for tenderness and resistance over the upper right rectus. The liver and spleen were not felt.

The leucocytes were 11,000 on admission, rising on the following day to 17,000, and remaining at about 20,000. There was a polymorphonuclear leucocytosis, no abnormal cells being found. Hb., 93 per cent; R. B. C., 4,600,000. The urine was negative. The Wassermann and Calmette 1 per cent and 5 per cent tests were negative. The temperature was irregular, at times intermittent, varying from 98° F. in the morning to 102° F. in the evening. A blood culture, made on October 10, yielded no growth. Nothing definite was found in the sputum, which was inconstant and small in amount. The X-ray of the chest showed only diffuse infiltration, with no evidence of effusion in the right pleura.

His condition continued the same, the pulmonary signs at the right base remaining indicative of a subdiaphragmatic abscess, rather than an intrapulmonary lesion. On October 11, the liver dulness was noted 7.5 cm. below the costal margin in the mammillary line, and 8 cm. below the ensiform. The liver edge was not felt.

On October 19, an exploratory puncture was made. A long needle was inserted in the 10th interspace in the posterior scapular line. At a depth of 8 cm. pus was encountered, and 5 cc. were withdrawn. It was thick, greyish green, and had a foul, pungent odor. No granules were noticed. Smears showed degenerated leucocytes and cells, and "fibrin and clot-like lumps." No tubercle bacilli and no amœbæ were seen.

On October 20, he was transferred to the surgical service and explored (Dr. McClure). A large abscess was found high in the right lobe of the liver, from which at least a liter of thick, greenish pus was evacuated. This pus had a foul, stinking odor. No amœbæ were found. The stomach and intestines were not observed. The temperature fell rapidly, and after November 7—17 days after operation—remained practically normal. There was free drainage by tube for about a week, and a small sinus persisted, which discharged pus freely.

On November 17, the patient insisted upon going home. He was up and about, feeling well, and declined further treatment. He had gained 16 pounds since operation.

The pus, which was aspirated before operation, was sent to the laboratory for culture. It was planted on the surface of various media anaerobically and aerobically, but most of it was inoculated into deep tubes of ascites-dextrose-agar, by the shake method of Rosenow. The surface plants yielded no growth after several weeks, but, at the end of four days, in-

numerable small, grey colonies were visible in the deep tubes. These were sharply localized in a zone about 1 cm. wide, and 2 cm. below the surface of the medium. These colonies showed in fresh and stained preparations a pure culture of a delicately branched, mycelial, spore-bearing growth, which seemed to belong to the streptothrix group.

The drainage from the operative wound was then immediately examined, and showed abundant dotted mycelial threads, apparently identical with those seen in the cultures. No granules were found in this material, and no radiating mycelia with peripheral clubs. There were numerous bacteria of many sorts, degenerated cells, and detritus.

Although the solitary liver abscess was the prominent feature of the case, a cryptogenetic infection seemed unlikely and a search was made for a portal of entry. No lesions were found on the skin, mucous surfaces, or in the special sense organs. The stools were normal, and there was no history obtainable to suggest gastrointestinal disease. On close questioning, the patient admitted that off and on, for about two years, he had had a slight cough, with occasional small lumps of sputum. The symptoms were so insignificant that there was more or less uncertainty in his description of them. When under our care he had no spontaneous cough, but after a good deal of effort was able to bring up a small amount of sputum. This specimen consisted of mucus, with opaque pinhead-sized lumps, which, on microscopic examination, were found to consist of degenerated pus cells. Throughout were scattered abundant threads exactly similar to those seen in the abscess discharge. No tubercle bacilli were found. Examination of the lungs at this time showed still considerable impairment of percussion at the right base behind, with faint breath sounds, and persistent fine crackles on inspiration. It was thought, however, that these sounds might depend entirely, or in part, upon the subdiaphragmatic condition.

An antigen was prepared by centrifuging a broth culture of the organism (see below), suspending the sediment in 10 volumes of salt solution, and extracting for 24 hours at 37° C. The clear supernatant fluid was used. With this antigen, the patient's serum fixed complement in amounts of 0.1 cc. Normal sera showed no fixation with four times this quantity, and the usual antigenic and anticomplementary controls were clear.

The case is to be looked upon, then, as one of chronic low-grade pulmonary streptothricosis, with a large, solitary liver abscess, from which has been isolated in pure culture the organism found in the sputum. The points of interest are the fulminating character of the hepatic involvement during the course of a practically latent pulmonary disease.

The cases of systemic streptothricosis up to 1912 are summarized in Petruschky's article in volume V of Kolle and Wassermann's *Handbuch der Pathogenen Microorganismen*, to which reference is made here. Whereas the portal of entry has quite frequently been through the respiratory tract, the metastases are usually generalized. We have found no reference to a solitary abscess of the liver, associated with true streptothrix infection.



# MORPHOLOGICAL AND CULTURAL CHARACTERISTICS OF THE ORGANISM.

The original tubes of ascites-dextrose-agar showed innumerable colonies located in a sharply demarcated zone about

2 cm. below the surface of the medium. The largest colonies reached a size of 1 mm. in diameter; they were grey, opaque, with a slightly darker center and slightly irregular edges. In the hanging drop, the growth was seen to consist of interlacing mycelial threads, not very highly refractile, non-septate, and single-contoured. The threads were about  $0.5\ \mu$  in diameter and dotted with highly refractile round bodies (spores) especially towards the periphery. True branching was easily and distinctly made out. There was no motility. There was no distinct radiating arrangement of the threads and no peripheral clubs.

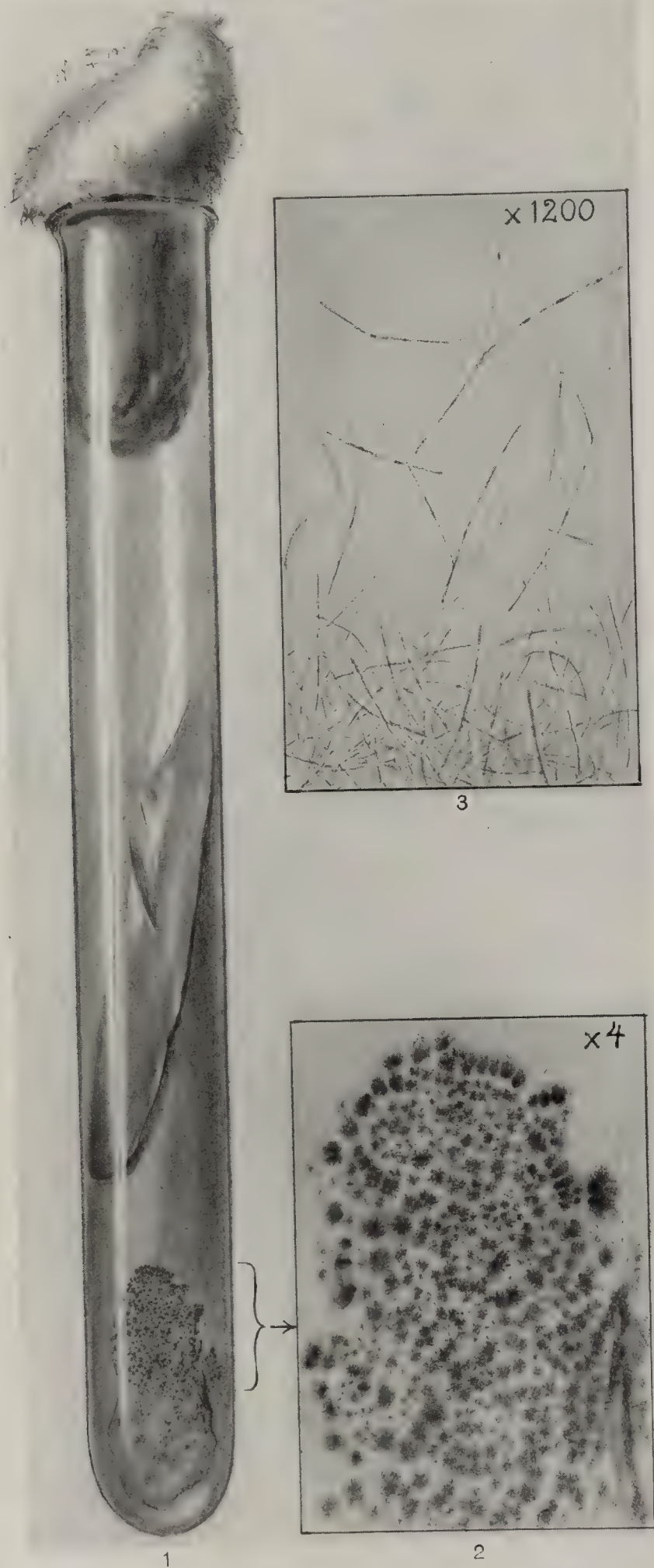
The organisms stained readily and well with carbol-gentian violet, methylene blue, Bismarck brown, and carbol-fuchsin. They decolorized completely and constantly when stained by Gram, and they were non-acid-fast.

These morphological and tinctorial characteristics have remained quite constant. The organism was subcultured aerobically and anaerobically on ascites-dextrose-agar, on dextrose-agar, plain agar, glycerine agar, blood agar, Loeffler's serum, potato, gelatin, and in plain and dextrose broth and milk. Up to this time, it has refused to grow on any of these media under completely aerobic or anaerobic conditions. A partial oxygen pressure seems necessary, and this has been furnished best by deep tubes of ascites-dextrose-agar, in which the colonies appear after 48 hours at a constant level below the surface. They increase in size until a maximal growth is reached at the end of from six to seven days. At this time, the colonies are about 1 mm. in diameter. They remain discrete. The most abundant growth has been obtained in ascites-dextrose-broth, partial pressure being secured by varying amounts of pyrogallie acid and alkali. Under these conditions, the colonies grow along the walls of the tube, subsequently dropping to the bottom. Individual colonies are easily fished from this medium. The cultures have all had a peculiar foul odor, similar to that of the original pus. Growth does not progress visibly at room temperature, body temperature being the optimum.

## ANIMAL INOCULATIONS.

Guinea-pig I. Male. Wt., 320 gm. October 26. Emulsion of one of the original agar tubes intraperitoneally. Nov. 1. Looks sick. Wt., 295 gm. Examination negative. Nov. 20. Looks well, active. Wt., 310 gm. Sacrificed. No lesions found.

Guinea-pig II. Male. Wt., 300 gm. Oct. 27. Emulsified growth from an ascites-dextrose-agar tube subcutaneously into left groin, and deep into hepatic region. Nov. 2. Looks sick, dull. Wt., 275 gms. A firm mass in left groin about 2 cm. in diameter—seems painful. Mass increasing rapidly in size. Explored under ether anaesthesia and found to be a necrotic gland, about 1 cc. of pus obtained. Smears show numerous threads identical with the original culture, and cultures yield the organism pure. Nov. 4. Wound in groin gapes—no tendency to heal, greenish necrotic lining, sero-sanguino-purulent discharge. Skin widely undermined. Animal looks sick. November 7. No change, streptothrix constant in the discharge. Nov. 20. Wound somewhat smaller, tendency to healing. Sacrificed. No internal lesions found.



1. Seven-day growth in ascites-dextrose-agar, showing deep situation of the organism.
2. Magnified four times, showing general grouping of the colonies.
3. Fresh specimen,  $\times 1200$ , showing branching and spores.



Guinea-pig III. Nov. 8. One loop of pus from G. P. II injected subcutaneously into left groin. Nov. 15. Fluctuating lump, 2 cm. in diameter, at site of injection. Aspirated; greenish brown pus, shows numerous bacteria and streptothrix threads. Nov. 21. Sacrificed. No other lesions found.

Guinea-pig IV. Male. 330 gms. Ascites-dextrose-agar culture into rt. jugular vein and subcutaneous tissue. Nov. 4. Wt., 305 gms., looks sick. Neck healed but marked induration; a chain of

firm glands, from .5 to 1.5 cm. in diameter, extending along right neck into mediastinum. Nov. 15. Gain in wt., glands smaller. Nov. 20. Sacrificed. No lesions found except chain of glands in right neck. Smears from glands negative for streptothrix.

The organism, then, seems to be of low pathogenicity for guinea-pigs, producing no general infection, but chronic localized lesions which tend to heal.

## PROCEEDINGS OF SOCIETIES.

### THE JOHNS HOPKINS HOSPITAL MEDICAL SOCIETY.

MARCH 1, 1915.

#### 1. Exhibition of a Case of Solitary Tubercle of the Brain. DR. HOWLAND.

R. J. (Col.), 3 years of age. This patient is the youngest of four children, one of whom died at 10 months of age, of pneumonia. The father and mother are young and strong. There have been no miscarriages or still births. There is no reason for suspecting lues and there is no history of exposure to tuberculosis.

He was a full term child, born without instruments after a very easy labor. He was fed at the breast for 14 months. There is no history of any illness during the first year. He had measles at 18 months and pertussis at 2½ years—neither very severe. He has suffered from no other acute infectious disease. There has been no trouble with his ears. He cut his first tooth at the fourth month; he walked well at the eleventh month and could talk at the seventeenth.

He seemed perfectly normal until August, 1914; at that time his mother noticed that he cried less than usual and he has not cried properly since. Just before Christmas it was noticed that his hands trembled when he was feeding himself; there was also some tremor of the body. It was noticed at this same time that, following a cold, his eyes began to droop and in about a week the ptosis was nearly as complete as it is now. Both sides were affected simultaneously. He has never had a nasal voice, regurgitation of food or paralysis of extremities, suggestive of diphtheria. He has grown very nervous and jumps at every noise. He has never had any convulsions. His mother has noticed no change in the child's mentality or in his disposition.

He was seen in the dispensary on February 4, when he could run about normally. He returned and was admitted on February 18. It was noticed that his ptosis was more marked and that it was difficult for him to walk. He has double ptosis, more marked on the right side, with ophthalmoplegia. He can move his eyes only to the slightest possible extent in any direction. His left eye has a tendency to turn in. His pupils are moderately dilated; they react very slightly, if at all, to light.

His tongue protrudes in the median line. When he attempts to cry it is seen that there is a slight loss of power on the left side of his face. He apparently hears equally well on each side. There is a marked tremor of his upper and lower extremities; he stands and walks now with considerable difficulty and this has distinctly increased.

He has no Babinski reflex or ankle clonus; his other reflexes are present and slightly exaggerated.

The course of his disease has been progressively and quite rapidly worse in the three weeks that he has been under observation.

It is obvious that he has something affecting the third, fourth and left sixth nerves and slight involvement of the left seventh. In addition, he shows Macewen's sign, *i. e.*, a change in the percussion note over the parietal regions, a curious cracked-pot

sound being elicited. The X-ray shows separation of the sutures and the digital markings characteristic of internal hydrocephalus.

The involvement of these nerves and the hydrocephalus would point to a lesion in the neighborhood of their nuclei, and a lesion which compresses or obliterates the aqueduct of Sylvius. A tumor is the most obvious explanation, it being hard to understand that a degeneration could produce the hydrocephalus. Dr. Dandy has made the interesting suggestion that it might be a tumor of the pineal gland pressing upon the corpora quadrigemina and the aqueduct.

In the last few days some new symptoms have appeared which seem to us to make the diagnosis more clear, that is, there has been a change in the cerebro-spinal fluid obtained by lumbar puncture. This, at the first puncture, contained 30 cells per cubic millimeter; at the second and third, 70 cells, almost all mononuclear, and in the fluid, on standing, a slight film develops.

It would appear that at the present time there is a certain degree of meningitis, which is progressing. The boy has a faintly positive von Pirquet. It seems to us, therefore, very probable that there is a solitary tubercle in the neighborhood of the nuclei of the third and fourth nerves; that this by pressure affects the third and fourth, sixth and seventh nerves; that it also produces hydrocephalus and that, secondarily, he is developing a tuberculous meningitis.

#### DISCUSSION.

DR. THOMAS: I have been most interested in this case, and Dr. Howland has been good enough to let me see it on a number of occasions. When the patient first came to the dispensary he presented a very different appearance. He then showed nothing but double ptosis with ophthalmoplegia, particularly of the upward movements of the eyes. Just before he came into the hospital he showed some difficulty in walking, and has more lately developed the symptoms of which Dr. Howland spoke. Dr. Dandy's suggestion of a tumor pressing on the corpora quadrigemina was most interesting. Indeed, the case has been most interesting from the start. I had never before seen double ptosis developing in a child, although the congenital form is not uncommon.

In Wilbrand and Saenger's "Neurologie des Auges," which is a veritable mine of medical literature, I find that they record a number of cases of acquired ophthalmoplegia in children in association with a certain number of acute diseases. Wichman has described one case in association with poliomyelitis. I was inclined to regard the condition in this patient as belonging to this unusual group until the other symptoms developed—the peculiar unsteadiness, the tendency to fall backwards, and the curious muscular tremor.

Tumors in the region of the corpora quadrigemina have engaged the attention of physicians ever since Nothnagel first called attention some 30 years ago to the fact that ophthalmoplegia, with difficulty in station and locomotion, often occurred in tumors in this region. The clinical symptoms of a tumor of the corpora quadrigemina, particularly involving the anterior pair, are ophthalmoplegia and the developing incoordination and inability to stand.



Ophthalmoplegia is easily understood by the involvement of the nuclei of the third and fourth nerves. The difficulty in standing is explained by an involvement of the paths from the cerebellum to the red nucleus. Many cases also show deafness, which is due to involvement of the posterior pair of the corpora quadrigemina, and this is often the most pronounced symptom in many of these cases. This child appears to hear well.

The condition of the pupils in such cases is always of great interest. The optic tract, after passing the chiasm, ends in three nuclei—the external geniculate body, the optic thalamus, and the anterior pair of the corpora quadrigemina. The part that appears to end in the corpora quadrigemina is thought by many to carry the fibers which have to do with the light reflexes, and it was hoped that lesions in this region would demonstrate this fact. This hope has not been fulfilled, as the pupils have been found very variously affected in these cases. In the present case the pupils are, I think, practically inactive to light.

The symptoms in this case which suggest involvement of the sixth and seventh nerves are not very pronounced, but if they are to be regarded it makes us think of the possibility of the lesion being a diffuse one at the base of the brain, for the nuclei of these nerves are relatively distant from the corpora quadrigemina. As Dr. Howland has told you, there are evidences of tuberculosis, and a solitary tubercle, in the region suggested by Dr. Dandy with secondary meningitis, seems the best explanation of the case.

## 2. Nutrition and Growth. (Abstract.) DR. LAFAYETTE B. MENDEL, New Haven, Conn.

It seems probable that the food requirement of the growing individual is in a measure specific. Special substances as well as certain proportions of lime, iron or protein are necessary. A comparison of the several food proteins and the tissue protein supposedly replaced or augmented by them excludes the possibility of any direct relationship between the two. In fact, proteins are no longer considered as entities in nutrition, but the significance of the protein *Bausteine* or nutrient units is emphasized. Much study is still needed to state which of the amino-acids or nutrient units of the proteins are indispensable. Glycocoll can be synthesized in the body and consequently a lack of it in the dietary would not be indicated by any nutritive disturbance. Tryptophan does not seem to be produced *de novo* by mammals and disastrous results follow the administration of a dietary free from it. Osborne and Mendel studied, in a diet in which the protein was the sole variable, the nutritive efficiency of various proteins, especially those of composition widely different from the normal tissue protein of the animals used. Rats were fed on a dietary to which isolated proteins in different concentrations were added. Normal growth was secured with some of the proteins, but not with others. The explanation of the failure is suggested by the known absence of certain amino-acids. The decline in growth caused by the lack of tryptophan or lysin can be checked promptly by the administration of these components. Restricted amounts of the necessary nutrient units will also reduce growth.

The absence of carbohydrate from the diet menaces nutritive functions in growth, but at present it is impossible to discriminate for or against any one of the usual dietary sugars.

The indispensability of the true fats seemed to be demonstrated. However, in the method used, lipoids, phosphatides, and vitamins were also removed from the food.

The growth of rats fed on protein-free milk, carbohydrate, and lard was suspended, but could be restored by the addition of unsalted butter, cod liver oil, or to a lesser degree by beef fat.

## DISCUSSION.

DR. JANEWAY: I can only say a few words of appreciation of what Dr. Mendel has said. Strange as it may seem to many of you, Dr. Mendel and I learned our physiological chemistry at

adjoining desks in Professor Chittenden's laboratory some twenty-odd years ago. In those days physiological was an adjective applied to chemistry. It was the ambition of Professor Chittenden that chemical physiology should grow up in New Haven, but it took the second generation to accomplish the fact. In that achievement, Professor Mendel has taken the lead. It is interesting, I think, to appreciate that the study of the individual plant proteins, in a very quiet way, in Professor Chittenden's laboratory and the nearby agricultural experiment station of Dr. Osborne, was really the start of all this work which Professor Mendel has presented to-night. For many years the work of Dr. Osborne was very little known. Now studies of nutrition, such as this work of Mendel and Osborne, are coming to bear strongly on a very interesting group of diseases—the so-called deficiency diseases. It is wholesome for us to find out that there is in the nutritional problem of normal growth something more than the provision of the mere energy requirement of the growing organism; and that there is a warrant for the belief—both in human pathology and in the physiology of the growing organism—that after all the instinct of the human race is going to be justified in the long run, and that we shall never be nourished on highly purified food products. For that outlook we have to thank Professor Mendel.

DR. WELCH: I should like to emphasize the fundamental importance of this work. The question of growth and what determines growth is of course at the bottom of not only physiological, but also of pathological, problems. I have felt that we never shall have an insight into the problems of pathological growth until the physiologists have given us a sound basis for the understanding of normal growth. Take, for instance, the most important of all pathological growths—cancer. In the last analysis, I am pretty well convinced that that is a question of an understanding of the factors concerned in growth. Take such work as Miss Maud Slye is doing now at the University of Chicago, where she has strains of mice with known pedigrees. In some strains there is no cancer, in others a certain percentage, and in still others something approaching 50-60 per cent developed cancer. She does not hesitate to speak of cancer as a mode of growth manifested as a hereditary phenomenon in some 50 per cent of the offspring of certain mice. What are the factors? Do they relate to what Dr. Mendel has spoken of as the inherited internal cellular factors, or do they relate to conditions around the cell—the environment? The former has been the usual idea. It is by no means certain that the wonderful capacity of cancer cells for almost indefinite growth does depend upon something inherent in the cell. I do not propose to attempt to develop the subject, except to thank Dr. Mendel for coming here and telling us of the results of this very important work, and to express the appreciation which I am sure all medical men and all pathologists feel for work of such a fundamental character.

Perhaps Dr. Winternitz will tell us something of the experiments he has recently been carrying on with chickens.

DR. WINTERITZ: The few experiments that Mrs. Winternitz has stimulated me to undertake have had more to do with maintenance than with growth. Dr. Goetsch succeeded in causing rats to mature much more rapidly and to bear much larger litters than normal by feeding hypophysis. We thought the gland might have a similar effect on chickens. The experiments were begun last spring and have been encouraging, inasmuch as the chickens born about the first of May and fed upon hypophysis developed about twice as rapidly as the controls and have been laying eggs regularly all winter. The controls began laying when they were between nine and ten months old. The animals were given a minute quantity of whole desiccated hypophysis. One ounce, I think, has been given to 12 chickens over a period of six months. They were much larger than the normal chickens for a long time. At present they are only slightly larger and exhibit no abnormalities.



Our experiments are in exact contradiction to some recently reported from the University of California by Dr. Wilson. When fed with fresh hypophysis her chickens developed much less rapidly. Their bones were fragile and the animals remained infantile in type.

MARCH 15, 1915.

**1. Observations on Cardiac Dyspnea. (Abstract.)** DR. F. W. PEABODY, Boston, Mass.

In cases of pure cardiac disease with decompensation, the dyspnea may be associated with a transient acidosis. In cardio-renal disease the acidosis is a more permanent feature. In neither type of case, however, does the determination of the alveolar carbon dioxid tension give evidence of a high degree of acidosis, and it is difficult to decide in how far the acidosis is a factor in producing the dyspnea. Experiments have been performed in which subjects rebreathe their expired air, so that the inspired air contains a continually increasing concentration of carbon dioxid. Normal subjects and cardiac or cardio-renal patients who have no acidosis react in approximately the same way to this added stimulus. Decompensated cases, on the other hand, with acidosis, are more sensitive, and become dyspneic with a much lower concentration of carbon dioxid. They would certainly be in like manner more easily affected by carbon dioxid or other acids produced in the body itself than are persons whose blood is normal. Thus the acidosis is at least one factor in the cause of the dyspnea.

**2. The Factors of Coagulation in Experimental Aplastic Anæmia. (Abstract.)** DR. S. H. HURWITZ, Boston, Mass.

In the course of a study on the factors of coagulation in a case of aplastic anæmia we were impressed with the analogy existing between the symptom-complex in this disease and that observed by Selling in three cases of benzol poisoning. Observations on the blood of our patient disclosed changes not only in the formed elements but also in the circulating prothrombin.

This clinical finding stimulated us to apply the methods, supplied by Howell's investigations, to a study of the factors of coagulation in the experimental aplastic anæmia of benzol poisoning. It was with the hope of throwing some light upon the hemorrhagic features noted in this intoxication that our experiments were undertaken; but as the work progressed, it seemed to give some additional information concerning the relation of the bone-marrow to the origin of some of the factors studied.

Our observations have shown that the clinical symptoms of rabbits poisoned with benzol, so far as the hemorrhagic tendency is concerned, give only slight indication of the profound changes which this myeloid tissue poison produces in the blood of these animals. Although the latter did not, in the majority of instances, show marked signs of hemophilia, a study of the blood usually revealed striking changes both in the formed elements and in the prothrombin-content.

So far as the effect of benzol upon the formed elements is concerned, our experiments confirm the work of Selling and of Duke. Following the administration of benzol, there is a rapid disappearance of the white cells from the peripheral circulation. The red blood corpuscles are much less affected than the white cells and the blood-platelets. The latter, however, may remain at a high level at a time when the white cells have almost entirely disappeared from the circulation.

Besides the formed elements, we have followed the factors of coagulation in the majority of our animals. These studies showed that benzol exerts an important influence in reducing the circulating prothrombin and that this substance is dependent for its production, in part at least, upon bone-marrow activity. The

two other factors of blood clotting—antithrombin and fibrinogen—were also followed. These were found to fluctuate but little from the normal.

Our results are in harmony with the recent proof that blood-plates contain prothrombin. They give additional evidence in support of the view that fluctuations in the amount of prothrombin may be produced by substances which affect the number of platelets, and that any toxin which produces a reduction in their number will simultaneously cause a diminution in the available prothrombin of the circulating blood. Our knowledge, moreover, of the origin of blood-platelets from the megakaryocytes of the bone-marrow emphasizes the importance of this tissue in maintaining the normal prothrombin equilibrium of the blood.

Although the marrow plays this important rôle in the elaboration of prothrombin, no definite parallelism could be established between the extent of bone-marrow injury, the number of blood-platelets and the relative amounts of prothrombin. This would suggest that it is not possible to create a dangerous prothrombin deficiency by a reduction in the number of blood-platelets alone and that some other tissue or tissues play some part in prothrombin formation.

**THE JOHNS HOPKINS HOSPITAL HISTORICAL CLUB.**

MARCH 8, 1915.

1. \* **Two Physician-Economists:** Sir William Petty, 1623-1687. Francois Quesnay, 1694-1774. (Illustrated.) DR. JACOB H. HOLLANDER.
2. \* **A Letter of Edward Jenner, Containing a Brief Account of His Discovery of Vaccination.** (Illustrated.) DR. CHARLES C. MCBRYDE, Washington, D. C.

**THE LAENNEC.**

MARCH 22, 1915.

1. **The Effect of Changes in Atmospheric Temperature Upon the Respiratory Tract.** DR. JAMES A. MILLER, New York City.
2. **The Rôle of Lymphocytes in Experimental Tuberculosis in Mice.** (Abstract.) DR. JAMES B. MURPHY, New York City.

This communication dealt with some interesting observations on the rôle of lymphocytes in tuberculosis experimentally produced in mice.

Dr. Murphy pointed out that the function of these cells had been underestimated, and indicated that the lymphocyte may be of primary rather than of subsidiary importance in resistance to infection with the tubercle bacillus.

Starting from the observations of Lewis and Margot that tuberculous animals develop large spleens, and that splenectomized animals infected three weeks after removal of the spleen survived the inoculation of tubercle bacilli longer than normal animals did, he sought an explanation of these facts.

With Dr. Lange he found that immediately after splenectomy the lymphocytes were decreased in number, whereas after 19 to 21 days the mice all showed a marked lymphocytosis. The author then confirmed Heineke's finding that the X-ray has an almost specific and immediate destructive action on the lymphoid system, and, in small doses, a minimal effect on other body cells.

Using splenectomy in some animals, the X-ray in others, a series of mice was available in which it was possible to note the influence exhibited by the lymphocyte in tuberculous infection, for in this series all gradations from a deficiency to an excess in the number of lymphocytes were present. The results of the inoculation of

\* To appear later in the BULLETIN.



such a series of mice with tubercle bacilli were illustrated by charts. The essential findings were that in mice, that had been splenectomized and X-rayed before inoculation, the duration of life was shortest; whereas, mice that had been splenectomized 3½ weeks before inoculation survived infection for the longest period of time.

As a result of his experiments, and supported by clinical evidence, Dr. Murphy drew the conclusion that the lymphocyte is an important factor in the resistance of animals to tuberculosis.

#### DISCUSSION.

DR. WINTERNITZ: Dr. Murphy is to be heartily congratulated on his interesting studies. The power of ridding the body of a type of cells like the lymphocyte with the X-ray and the leucocyte with benzol has opened very broad fields for study.

Dr. Murphy has pointed out to-night the important rôle played by the lymphocyte in infectious granuloma. At a previous meeting of this Medical Society he indicated that the lymphocyte was equally important in the protection of the body against the invasion of tumors and I am sorry he has been unable to tell us more of this work to-night.

One confusing point has occurred to me concerning which I should like to question Dr. Murphy if I may? If the leucocyte is so potent in the protection of the body against tuberculosis, why does this infection lodge by preference, as it seems, in the lymphadenoid tissue?

DR. MURPHY: In answer to Dr. Winternitz's question on the involvement of the lymph glands in tuberculosis, I would say that we have, of course, considered this point. It will certainly require further investigation for a direct explanation. A number of theoretical suggestions might be brought forward as reasons for this frequent location of the infection. The lymph glands, as we know, act as filters for the materials getting into the lymph spaces. These are supposed to be common portals of entry for the tubercle bacilli. In the average individual these are taken care of, while in other individuals, either on account of a more virulent organism or a broken down resistance, the infection establishes itself. As a matter of fact, we know in general that tubercular infections of the lymph glands progress less rapidly than most of the other types.

DR. WINTERNITZ: Of course, the question of the spleen enters here. It is the abdominal organ most frequently affected by tuberculosis.

DR. MURPHY: In my experience the spleen is involved only in overwhelming infections. Here, as in lymph gland involvement, we can only theorize. The fact that the bone-marrow is involved often in certain pyogenic infections is not accepted as proof that the polymorphonuclear leucocyte has no function in the protection of the body against these types of organisms. The action of this cell is generally accepted. It seems to me that we have as strong, if not stronger, proof that the lymphocyte is just as important an agent of defense against the tubercle bacillus as is the polynuclear cell against certain other infections.

### NOTES ON NEW BOOKS.

*Chemical Pathology.* By H. GIDEON WELLS, PH. D., M. D., Professor of Pathology in the University of Chicago and in Rush Medical College, Chicago; Director of the Otho S. A. Sprague Memorial Institute. Second edition, thoroughly revised. (Philadelphia and London: W. B. Saunders Company, 1914.)

The first edition of this volume has more than answered the purpose of the author; that is, it has furnished collateral reading in chemistry for the student of general pathology; it has correlated the chemical and physiological advances in medicine for the graduate; it has been a source of information to the investigator in biological chemistry and scientific medicine where these fields overlap; and, above all, it has answered as a guide to the original sources of our knowledge of these subjects.

To those who have been familiar with this book the appearance of the second edition will be greatly appreciated. The chemical study of biological problems has greatly increased in the past seven years, and the many substantial additions to the literature on the subject will be found classified and summarized in this volume.

The plan of the book is essentially that of the former one. Many portions have been largely or entirely rewritten, in accordance with the growing knowledge on the subject.

The careful selection of references throughout the volume makes a full bibliography of each subject readily accessible. The book remains unique in the English language and will continue to be a valuable aid to the student as well as to the investigator in scientific medicine.

*Diseases of the Rectum and Colon and Their Surgical Treatment.* By JEROME M. LYNCH, M. D. (Philadelphia and New York: Lea & Febiger, 1914.)

This volume is dedicated to the late Dr. J. P. Tuttle, with whom Dr. Lynch was associated and whose professorship in the New York Polyclinic Medical School he now occupies. Approximately the first half of the book is devoted to a consideration of the

rectum and the anus; the latter half deals with the colon. The general plan of this volume is much like that of numerous other treatises upon the same subject. The author has, however, omitted the usual lengthy first chapter dealing with anatomy and physiology. This omission is decidedly an advantage, inasmuch as the facts contained in such chapters are easily accessible in any ordinary text-book on anatomy and add nothing of value to such clinical subjects as properly form the objective of a clinical text-book.

The first three chapters of Dr. Lynch's work are devoted to general subjects: Examination, Preparation of the Patient, and Anesthesia. Under the heading of Anesthesia a very sane valuation of local anesthetic methods is presented, the discussion being notably conservative and free from the rather extravagant advocacy of local anesthesia, which is just now rather popular. The most interesting feature of this particular chapter is the discussion of the author's method of extradural or sacral anesthesia. This consists in the introduction into the sacral canal of anesthetic fluids, which are designed to produce regional anesthesia. The idea is a very promising one and gives rise to the hope that its further development and practice will provide a valuable form of local anesthesia for this whole field of surgery. One is forced to regret, however, that the description of the technique employed is not entirely clear and there is not a sufficient volume of successful cases recorded to convince one, as yet, of its practical success.

Following the first three chapters the usual rectal diseases are given in order and the text is well supported by numerous illustrations. Many of the author's cases are of great interest, particularly those described under the heading of Malformation. The diseases of the colon are also handled in the same general manner and there are a number of excellent colored plates illustrating proctoscopic findings. The subject of cancer, which, of course, is one of paramount importance, receives ample consideration, much of the unnecessary and commonplace being omitted. In this chapter the author describes the blocking of the sympathetic



nervous system at the pelvic brim to reduce the shock in radical operations. There is an excellent illustration of a dissection of the lower abdominal and sacral sympathetic in connection with this phase of the operative procedure.

Finally, there are chapters on the use of serums and vaccines and also of X-ray examinations of the intestine. The book as a whole is readable and evidently is based upon a wide practical experience in this field of surgery. The illustrations, as before noted, are numerous and of good quality, and there is a comprehensive index. The technical perfection of the work is somewhat impaired by lack of careful proof-reading, as is instanced in the chapter on cancer, in which several sentences are made to read quite differently from what is the obvious intention. As a whole, however, the book is decidedly better, both as a practical aid and as a scientific study of this subject, than any of the other treatises of similar character which have appeared within the last few years.

*Cystoscopy and Urethroscopy.* By LEWIS and MARK. Cloth, \$4.50. (Philadelphia: Blakiston & Co., 1915.)

The first portion of the book is devoted to a historical review of the development of cystoscopy and the various types of cystoscopes. A detailed description of the instruments and the technique of cystoscopy occupies a considerable portion of the volume. The development of urethroscopy is reviewed and there is a more or less detailed description of the different lesions which are to be found in the various portions of the urethra, together with rather good illustrations. Probably the most valuable portion of the volume is the chapter by Braasch in which he gives a concise, clear description of the changes in the pelvis in various kidney lesions, together with pyelogram illustrations.

The book contains many practical points which will be found useful for students. J. T. G.

*John Shaw Billings: A Memoir.* By FIELDING H. GARRISON, M. D. Illustrated. (New York: G. P. Putnam's Sons, 1915.)

The subject of this memoir possessed a commanding physical and mental personality which compelled respect and attention at all times. Born in Indiana in 1838 in the conditions of pioneer life and early thrown upon his own resources, by indomitable courage and force of character he gained, largely by his own exertions, a college training at Miami University, and medical training at the Ohio Medical College, two institutions, neither of which had then or now have a high standard of scholarship. Their work, however, was supplemented by the initiative and force of character of the diligent student, who learned thoroughly what to study and how to study. He entered the United States Army Medical Corps as a contract surgeon in the autumn of 1861 and was appointed lieutenant and acting surgeon in April, 1862. For more than two years he saw active service as an operating surgeon and in charge of army hospitals, mostly at the front in the Civil War. He shared in the arduous work at Gettysburg, Chancellorsville, in the battles of the Wilderness and before Petersburg. In 1864, however, because of his known and proved ability as a medical statistician and student of medicine, he was ordered to Washington to engage in special duties in the surgeon general's office, and there remained almost continuously until he was retired at his own request from the service in 1895. In Washington he became known as a sanitarian, an expert in vital statistics, an authority on ventilation, hospital construction, organization and medical education, a bibliographer and librarian, the creator of the most extensive medical library in the world and head of the Army Medical Museum. After his retirement from the army medical corps he became professor of hygiene in the University of Pennsylvania, but not for long. He was soon called to New York to take charge of the combined Tilden, Astor

and Lenox Libraries which had become the New York Public Library and remained there until his death in 1913, after 17 years of service.

During this period of more than 50 years his wonderful mental activity is shown by his record of army service and by his bibliography which presents 171 titles of books and elaborate papers. He possessed the faculty of accomplishing his work rapidly with a maximum of results and a minimum of friction and lost motion. To the readers of the BULLETIN probably the chapter on his connection with the plan and building of The Johns Hopkins Hospital will make an especial appeal. Although Dr. Garrison has not added much to this chapter which was not already known to a few persons, he has brought out most interestingly the fact that Dr. Billings had preponderant influence not only in the adoption of the building plans, but also in shaping the organization of the different departments and in the selection of the heads of them like Welch, Osler, Halsted and others.

Dr. Garrison has written the memoir in a sympathetic spirit and has given interesting glimpses of Billings' character by extracts from his letters and note-books. He is thus shown as an affectionate husband, a fond father, an earnest student, a public-spirited officer of the government, cheerfully doing extra and uncompensated service in the census, in vital statistics, in marine hospital reorganization and in public duties at home and abroad. It was a busy, active and productive life. He was clearly the most forceful personality which the army medical corps has produced. His story is most interesting and inspiring. H.

*A Laboratory Manual and Text-Book of Embryology.* By CHARLES W. PRENTISS, A. M., PH. D., Professor of Microscopic Anatomy in the Northwestern University Medical School, Chicago. Octavo, of 400 pages, with 368 illustrations, many of them in colors. Cloth, \$3.75. (Philadelphia and London: W. B. Saunders Company, 1915.)

Primarily a brief text-book of human embryology, in that sense it is based largely on the Manual of Human Embryology of Keibel and Mall. Dr. Prentiss has made his book practicable as a laboratory guide for medical students by basing the account of the segmentation stages on the amphioxus and frog's eggs; the development of the primitive embryo on the chick; and the general organology on various dissections and sections of pig embryos which represent the author's own experience. Thus he uses comparative anatomy on the basis that it gives available laboratory material, which he has welded together and related to human embryology. The author has drawn largely from the literature and wisely avoids repeating long literature lists which are covered by the Keibel-Mall manual. Of the 368 illustrations approximately one-third are new drawings. About sixty of the new drawings are of dissections and semi-diagrammatic reconstructions, of which those on the chick in the third chapter may be mentioned as especially instructive.

The text gives a brief but clear account of embryology and emphasizes organology, which makes so valuable a foundation for anatomy for the medical student. Dr. Prentiss' manual can be recommended as meeting a real need of the medical student in that it will give him a valuable introduction to the subject of human embryology. F. R. S.

*Nature and Nurture in Mental Development.* By F. W. MOTT, M. D., F. R. S. Cloth, \$1.50. (New York: Paul B. Hoeber, 1915.)

This small book of 137 pages is an amplification of three Chadwick Trust lectures delivered last year.

The subject is a very vast one, but the matter is arranged in a simple, concise and helpful way. An idea of the scope of the book may be readily seen when one finds such things considered as (a)



Mental Hygiene from a Physiological Standpoint, (b) Causes of Mental Deficiency, (c) The Raw Material of Character in Relation to Heredity, (d) Genius in Relation to Heredity, (e) Sex in Relation to Character, Crime and Insanity, (f) The Influence of Nutrition and The Influence of Education in Mental Development, (g) Sex and Education. The above are only a few of the interesting items dealt with, but no doubt they will be sufficient to stimulate those interested to inquire further.

Emphasis is laid on the rôle of the sex glands in development, and the author believes that the suppression of the normal physiological processes of reproduction and of the maternal instinct of women is one of the pressing problems of civilization.

Dr. Mott admits that there are a few individuals of very defective intelligence who may be looked upon as born criminals, but he disagrees with the views of Lombroso and tries to show how crime is much more a matter of opportunity and environment.

One is glad to see that such a firm attitude is taken in regard to the care of the feeble-minded, and it is pointed out how, so far as the community is concerned, the higher-grade imbecile is a grave danger. A strong plea is entered for the early segregation of all mentally defective children.

There are some statements in the book with which we cannot agree. To quote a single instance: "The deeper the dementia (loss of mind) the greater are the number of nerve cells and fibers destroyed or undergoing decay and destruction" (page 24).

On the whole, however, the author's point of view is a very sound one, and the book can be heartily recommended.

D. K. H.

*Nursing and Care of the Nervous and the Insane.* By CHARLES K. MILLS, M. D. Third Edition, revised by the author, assisted by N. S. YAWGER, M. D. (Philadelphia and London, J. B. Lippincott Company, 1915.)

This little book by the well-known Philadelphia neurologist contains the substance of a course of lectures delivered to nurses. In the first chapter some of the personal qualities and qualifications of nurses who deal with nervous patients are touched on, and advice is given in regard to the nursing in cases of hysteria, epilepsy and similar conditions. In the second, third, and fourth chapters the use and technique of massage, hydrotherapy, and electricity are treated of; in the fifth are to be found more or less general rules to be followed in the care of insane patients.

The book is somewhat narrow in its scope, and cannot be particularly recommended.

*Dissection Methods and Guides.* By DAVID GREGG METHENY, M. D., etc. Cloth, \$1.25. (Philadelphia: W. B. Saunders Company, 1914.)

This small book is an addition to the list (already large) of laboratory manuals which are designed to guide the student in the preparation of the various regions of the human cadaver, in order that the study of their component structures may be facilitated and undue mutilation be avoided. It is a compact and well-printed volume of 131 pages, in which the work of dissection is systematically laid out, the surface incisions being indicated by means of twelve simple illustrations. The outline has been planned so that work may be started with equal advantage on any part of the body. One good point is the absence of structural description, which makes necessary the consultation of standard text-books and atlases of anatomy; indeed, the author states that his guide is "designed for use in conjunction with a text-book, but it is not to supplant it in any way."

The practice of employing the old nomenclature in the text and of relegating the B. N. A. to brackets is a reversal of that usually followed, and is to be deplored, as tending to push unduly into the future the universal adoption of a single system of terminology.

Though it participates in the defects inseparable from all such guides, the book supplies a fairly good outline of some of the procedures to be followed in acquiring a knowledge of the morphology of the human body.  
C. C. M.

*Development and Anatomy of the Nasal Accessory Sinuses in Man.* By W. B. DAVIS. Cloth, \$3.50. (Philadelphia: W. B. Saunders Company, 1914.)

We must apologize to the author and the publishers for the long delay in reviewing this admirable book. A vast amount of painstaking work has been done by the author in collecting and preparing such a fund of material, in making measurements, noting anomalies, and describing other points of interest in the 290 anatomical specimens upon which the observations in the book are based.

The internist as well as the specialist should read this book, or at least study the series of beautiful drawings made by Miss Peters. To the teachers, especially, this book is warmly recommended. If the series of drawings are removed and properly grouped, they demonstrate very closely the various stages of development of all of the accessory sinuses and the relation of each of these sinuses to all the important surrounding structures. From a careful study of these can be obtained a better understanding of the various anomalies which are frequently encountered in clinical work.

In the laryngological dispensary of The Johns Hopkins Hospital these drawings, together with the appropriate legends, have been grouped and placed on the walls, so that the students and physicians may constantly refer to them.

*The Interpretation of Dreams.* By PROF. SIGMUND FREUD. Authorized translation of third edition, with introduction by A. A. BRILL. Cloth, \$4.00. (New York: The Macmillan Company, 1913.)

Some idea of the increase of interest in the study of the psychoneuroses may be gleaned from the fact that whereas nine years elapsed between the first and second editions of this book only a little more than a year has gone by before the need for the third and present edition has arisen.

Since the appearance of the first edition the author's experience has induced him to lay even more weight on the significance of symbolism in dreams and consequently a number of foot-notes have now been added and numerous insertions have been made in the text.

In discussing Freud's work, a very common criticism is that little value should be placed on dreams, which are the product of psychoneurotic or diseased minds, and no doubt at the start it is well to emphasize the fact that Freud has forestalled the above objection by using his own dreams as examples of the points which he wishes to elucidate.

In Chapter I the scientific literature on the problems of the dream is fully and convincingly discussed and the great diversity of the views expressed in regard to the importance and non-importance of dreams is clearly put forth.

Freud believes that it may be taken as an indisputable fact that all the material composing the content of the dream has originated in experience, "but the connection has frequently to be carefully sought." He believes that the dream is an occurrence of our own psychic activity and that it thinks, especially in visual pictures, but also in auditory and other special sense impressions.

In the farther chapters of this interesting book Freud attempts to prove his assertions. With numerous striking examples he shows how a dream represents a wish as fulfilled and asserts that such is a universal and not merely an accidental characteristic. He frankly admits that superficially many dreams may seem to have a painful content, but that this is simply due to the fact that people do not differentiate between the manifest and latent content.



Upon analysis painful and fearful dreams may also be discovered as wish-fulfillments. There are many points and statements in the book that, with all due respect to the enormous experience and ingenuity of the author, one would hesitate to accept unreservedly, but these do not especially detract from the stimulating character of the book.

*Diseases of the Skin.* By FRANK CROZER KNOWLES, M. D. With 199 illustrations and 14 plates. (Philadelphia: Lea & Febiger, 1914.)

This volume compares favorably with other text-books of its class, but shows no material difference. There are the usual chapters on anatomy, physiology, general symptomatology diagnosis and treatment.

Diseases of the mucous membranes and the discussion of the eruptive fevers are dealt with in separate chapters.

The various methods of treatment from which the author himself has had the most satisfactory results are given and much profit can be obtained from reading these sections. In addition, the special and more recent remedies, such as vaccines, radium, the various electric appliances, refrigeration, etc., are dealt with. In an appendix are added numerous adjuvants, which are often found useful in dealing with cases of skin disease.

The descriptions of the various eruptions are clear and sufficiently complete; the points in differential diagnosis are well made. The various tests for syphilis and tuberculosis are outlined.

The illustrations, though numerous and well selected, have not been reproduced well; they are lacking in clearness and definition.

*Morris' Human Anatomy.* Edited by C. M. JACKSON, M. S., M. D. Fifth edition. \$6 net. (Philadelphia: P. Blakiston's Son & Co., 1914.)

The book as a whole differs but little from its immediate predecessors, although reforms already initiated in the fourth edition have been extended. Small print for matters of general interest is more used. This not only facilitates reading, but it has also permitted the editor to enlarge the scope of the work and to insert many additional illustrations without making it cumbersome by adding to its bulk. The B. N. A. system of nomenclature is more generally employed than in the former edition. Several new departures have been made, as, for example, the insertion at the end of most of the sections of important references to the literature on the subject, so that the student can look up easily detailed information on topics which have interested him. It is to be hoped that in the next edition still more references of this sort will be given, particularly on the side of comparative anatomy. The insertion of illustrations of microscopic preparations leads to a valuable correlation of the gross findings with microscopic structure. A tendency is also evident, in some places, to lay increasing stress upon the functional rather than upon the purely morphological aspect of the subjects treated.

Many of the sections into which the book is divided have been written by authors who did not participate in the fourth edition. These sections have been much more changed than those revised

by the same authors. The change is noticeable in the general scientific attitude, and in the point of view, rather than in the details of description, which must necessarily remain about the same. Professors Gunn, Huber, Jacobson, Morris and Sabin have withdrawn and Professors Clark, Jackson, Jones, Morley, Senior and Waterston have taken their places. The new work on the relative growth of the different parts of the body and on cytomorphosis has been incorporated in the section on morphogenesis. The recent advances in our knowledge of the growth of lymphatics are also discussed. It is to be regretted that the advances which have lately been made by comparative neurologists in the interpretation of the plan of architecture of the human central nervous system have not been mentioned in detail. The section dealing with the digestive system has almost doubled in size. Space has been devoted to the discussion of the teeth (not given in the old edition), and the facts brought to light by recent experimentation with Roentgen rays relative to the form and position of the stomach and other viscera have been stated. Finally, the clinical and topographical anatomy has been strengthened by the insertion of many figures from X-ray photographs and by reference to operative procedures on the hypophysis and other structures.

E. V. C.

*Text-Book of Surgical Operations for Physicians and Students.* Illustrated by Clinical Observations. By PROF. FEDOR KRAUSE, Privy Medical Councillor, Directing Physician, Augusta Hospital, Berlin. In association with EMIL HEYMANN, M. D., Chief Physician, Augusta Hospital. Translated into English and edited for American readers by ALBERT EHRENFRIED, A. B., M. D., F. A. C. S. Assistant Visiting Surgeon, Boston City Hospital, etc. In six volumes. Vol. I. Cloth, \$6.00. (New York: Rebman Company, 1915.)

The translator in his preface says that the book is primarily a text-book of operative surgery. It deals with the subject entirely from the personal viewpoint of its distinguished author, except where the translator has modified the text to suit American conditions. It approaches its subject in a novel way by the presentation and discussion of actual cases, which are carefully followed from the beginning through the operative treatment, to the end result.

The 260 pages are divided into 12 chapters. General surgical technic is considered in the first four. In the remaining chapters the surgery of the head is taken up as follows: Wounds of the head; extirpation of tumors in tissues of the face; plastic operations on the face, and special plastic procedures; the eye and orbit; the ear; the nose and accessory sinuses; the trifacial nerve. The appearance of the book is very inviting, with its attractive cover, thick paper, good print, wide margins, and graphic illustrations.

Judging from the contents of the first volume, one might be inclined to think that there would be more volumes than the amount of text justifies. In other words, if the same material were published in three, or possibly two, volumes, without any diminution in its value, it would reach a very much larger number of students and working surgeons, than in its present elaborate form.

J. S. D.

## BOOKS RECEIVED.

*Reducing Weight Comfortably: The Dietetic Treatment of Obesity.* By Prof. Gustav Gaertner, M. D. Authorized translation in English. 1914. 12°. 313 pages. J. B. Lippincott Company, Philadelphia and London.

*The Heart in Early Life.* By G. A. Sutherland, M. D., F. R. C. P. 1914. 12°. 211 pages. Henry Frowde, London; Hodder & Stoughton, London; Oxford University Press, New York.

*National Association for the Study of Pellagra.* Transactions of the Second Triennial Meeting at Columbia, S. C., October 3 and 4, 1912. 1914. 8°. 409 pages. The R. L. Bryan Company, Columbia, S. C.

*Clinical Society of the University of Michigan.* Transactions, October, 1913–October, 1914. Vol. V. Edited by the Secretary-Treasurer. 1914. 8°. 175 pages. Ann Arbor, Mich.



*Mechano-Therapeutics in General Practice.* By G. de Swietochowski, M. D., M. R. C. S. With 31 illustrations. 1914. 12°. 141 pages. Paul B. Hoeber, New York.

*Child Training as an Exact Science.* A Treatise Based upon the Principles of Modern Psychology, Normal and Abnormal. By George W. Jacoby, M. D. With illustrations. 1914. 12°. 384 pages. Funk & Wagnalls Company, New York and London.

*Acute General Miliary Tuberculosis.* By Professor Dr. G. Cornet. Translated by F. S. Tinker, B. A., M. B., B. C., M. R. C. S., L. R. C. P. 1914. 8°. 107 pages. Paul B. Hoeber, New York.

*A Text-Book for Midwives.* By John S. Fairbairn, M. A., B. M., B. Ch. (Oxon.), F. R. C. P. (London), F. R. C. S. (Eng.). With 3 plates and 104 illustrations, 5 in color. 1914. 8°. 317 pages. Henry Frowde, London; Hodder & Stoughton, London; Oxford University Press, New York.

*Evolution of Sex in Plants.* By John Merle Coulter. 1914. 12°. 140 pages. The University of Chicago Press, Chicago, Ill.

*Royal College of Surgeons of England.* Calendar. 1914. 8°. 400 pages. Taylor and Francis, London.

*Report of the Surgeon General, U. S. Army, to the Secretary of War.* 1914. 8°. 306 pages. Government Printing Office, Washington.

*Ohio State Board of Health.* Twenty-eighth Annual Report of the State Board of Health of the State of Ohio. For the year ending December 31, 1913. 1914. 8°. 899 pages. Columbus, Ohio.

*Carcinoma of the Thyroid in the Salmonoid Fishes.* An Investigation and Experimental Study Conducted Jointly by the Gratwick Laboratory of the State Institute for the Study of Malignant Disease, Buffalo, N. Y., and the United States Bureau of Fisheries. By Harvey R. Gaylord, M. D., and Millard C. Marsh. With the collaboration of Frederick C. Busch, M. D., and Burton T. Simpson, M. D. Publications from State Institute for the Study of Malignant Disease. Serial No. 99. Issued April 22, 1914. 4°. Government Printing Office, Washington.

*Text-Book of Massage and Remedial Gymnastics.* By L. L. Despard. Second edition. 1914. 8°. 413 pages. Henry Frowde, London; Hodder & Stoughton, London; Oxford University Press, New York.

*Therapeutics of the Circulation.* By Sir Lauder Brunton, Bt., M. D., D. Sc., LL. D. (Edin.), LL. D. (Aberd.), F. R. C. P., F. R. S. Second edition. With illustrations. 1914. 16°. 536 pages. Paul B. Hoeber, New York.

*Lead Poisoning: From the Industrial, Medical and Social Points of View.* Lectures delivered at the Royal Institute of Public Health. By Sir Thomas Oliver, M. A., M. D., M. R. C. P. 1914. 12°. 294 pages. Paul B. Hoeber, New York.

*Public Health Laboratory Work.* By Henry R. Kenwood, M. B., F. R. S. Edin., D. P. H., F. C. S. Sixth edition, with illustrations. 1914. 8°. 418 pages. Paul B. Hoeber, New York.

*International Clinics.* A Quarterly of Illustrated Clinical Lectures and Especially Prepared Original Articles. By leading members of the medical profession throughout the world. Edited by Henry W. Cattell, A. M., M. D. Vol. IV. Twenty-fourth series. 1914. 8°. 314 pages. J. B. Lippincott Company, Philadelphia and London.

*Fever: Its Thermotaxis and Metabolism.* By Isaac Ott, A. M., M. D. 1914. 12°. 166 pages. Paul B. Hoeber, New York.

*Selected Addresses on Subjects Relating to Education, Biography, Travel, etc.* By James Tyson, M. D., LL. D. [1914.] 12°. 366 pages. P. Blakiston's Son & Co., Philadelphia.

*United States, Treasury Department.* Annual Report of the Surgeon General of the Public Health Service of the United States. For the fiscal year 1914. 8°. 357 pages. Government Printing Office, Washington.

*Laboratory Manual for the Detection of Poisons and Powerful Drugs.* By Dr. Wilhelm Autenrieth. Authorized translation of the completely revised fourth German edition by William H. Warren, Ph. D. With 25 illustrations. [1914.] 8°. 320 pages. P. Blakiston's Son & Co., Philadelphia.

*E. Merck's Annual Report of Recent Advances in Pharmaceutical Chemistry and Therapeutics.* Vol. XXVII, 1913. 1914. 8°. 589 pages. E. Merck, Chemical Works, Darmstadt.

*Interstate Commerce Commission.* Twenty-eighth Annual Report (in two parts). Part I. December 1, 1914. 8°. 178 pages. Government Printing Office, Washington.

*Medical Diagnosis.* By Arthur Latham, M. A., M. D. (Oxon.), F. R. C. P. (Lond.), and James Torrens, M. B., B. S. (Lond.), M. R. C. P. (Lond.). With 74 illustrations; 19 in color. 1915. 8°. 641 pages. Macmillan Company, New York.

*A Handbook of Fevers.* By J. Campbell McClure, M. D. (Glasgow). 1914. 8°. 470 pages. Paul B. Hoeber, New York.

*Der Starrkrampf, seine Entstehung und Behandlung.* Von Prof. Dr. Ferdinand Blumenthal. 1914. 12°. 79 Seiten. Urban & Schwarzenberg, Berlin u. Wien.

*Praktikum der Chirurgie.* Von Dr. O. Nordmann. I Teil. Allgemeine Chirurgie. Mit 90 teils farbigen Abbildungen. 1915. 8°. 216 Seiten. Urban & Schwarzenberg, Berlin-Wien.

*Seuchenentstehung und Seuchenbekämpfung.* Von Prof. Dr. F. Neufeld. Mit 24 Abbildungen. 1914. 12°. 204 Seiten. Urban & Schwarzenberg, Berlin-Wien.

*Augenverletzungen im Kriege und ihre Behandlung.* Mit einem Abriss über die Diagnose und Behandlung des Trachoms. Mit 46 Abbildungen. 1914. 12°. 96 Seiten. Urban & Schwarzenberg, Berlin-Wien.

*Text-Book of Surgical Operations.* By Prof. Fedor Krause, in association with Emil Heymann, M. D. Translated into English and edited for American readers by Albert Ehrenfried, A. B., M. D., F. A. C. S. In six volumes. Vol. I. With 55 plates having 233 illustrations in two or more colors and 61 figures in the text. 1915. 4°. 267 pages. Rebman Company, New York.

*The National Association for the Study and Prevention of Tuberculosis.* Transactions of the Tenth Annual Meeting, Washington, D. C., May 7-8, 1914. 8°. 448 pages. Wm. F. Fell Company, Philadelphia.

*Congress of American Physicians and Surgeons.* Transactions of the Congress of American Physicians and Surgeons. Ninth triennial session, held at Washington, D. C., May 6 and 7, 1913. 8°. 104 pages. New Haven, Conn.

*American Surgical Association.* Transactions of the American Surgical Association. Vol. XXXII. Edited by Archibald MacLaren, M. D. 1914. 8°. 713 pages. Philadelphia.



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## BULLETIN

OF

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## AN ATTEMPT TO IMMUNIZE CALVES AGAINST TUBERCULOSIS BY FEEDING THE MILK OF VACCINATED COWS.

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The question of the transmission of immunity from parent to offspring—paternal transmission, maternal transmission, placental transmission and transmission through milk—has long occupied investigators and there is an extensive literature on the subject. Experiments have been made on human beings, horses, cows, goats, dogs, cats, rabbits, guinea-pigs, mice and fowls. In the greater number of the experiments antitoxic immunity has been investigated, as more exact quantitative experiments are possible with this form of immunity, but the work has not been confined to any one line and there have been many experiments reported on the transmission of agglutinins, lysins, precipitins, and other immune bodies. While there are some discordant results in the literature, it may be accepted as proven that an efficient immunity may be established against a number of infectious and toxic agents; that in the case of most of these immune bodies can be demonstrated in the blood; that these immune bodies may also appear in the milk; that from the milk they may be absorbed from the alimentary canal of the nursling and appear in the blood of the latter, where they exert a definite protective influence.

I shall make no attempt to give a complete review of the literature, but quote only a few authors in support of the above statement. Ehrlich<sup>1</sup> showed that immunity against abrin in mice could be transmitted through the milk to the young. He concluded that the immunity thus transmitted was passive; that it increased with the time of nursing and lasted two or three months. Ehrlich and Huebner<sup>2</sup> were able to show the transmission of immunity against tetanus in pigs and mice from mothers to nurslings.

Widal and Sicard<sup>3</sup> found that typhoid agglutinin, as well as the antitoxins of ricin, abrin and tetanus, may be transferred in mice through the milk of immune mothers to their young. Similar experiments with cats and guinea-pigs gave negative results.

Felice La Torre<sup>4</sup> made observations on 17 mothers who nursed 17 children. The ages of the children ranged from 1 to 24 months. The mothers all received diphtheria antitoxin after the birth of the children, 5 receiving three subcutaneous injections of 3000 units, a total of 9000 units each, and the remainder, three injections of 6000 units, a total of 18,000



units each. The blood-serum of the children was examined before the mothers received antitoxin and again three days after the last injection. In every case, regardless of age, a transference of the specific antibodies to the blood of the children could be demonstrated, but in such small quantities that the author did not consider this method of value either for prophylactic or curative purposes.

Römer and Much<sup>8</sup> showed that tetanus antitoxin, injected subcutaneously into cows, was capable of being transmitted through the milk to young calves and could be demonstrated in the blood of the latter.

Much<sup>8</sup> demonstrated the transmission of tetanus antitoxin through the milk from human mothers to their infants.

Hamburger<sup>7</sup> injected tetanus antitoxin into a rabbit three hours after she had given birth to young and was able to demonstrate antitoxin in the rabbit's milk and subsequently in the blood of the young rabbits fed on this milk.

Hamburger<sup>8</sup> repeated some of Ehrlich's experiments and was able to confer a high grade of immunity to young mice against ricin by causing them to nurse immune foster-mothers.

Römer<sup>9</sup> demonstrated the transmission through the milk of tetanus antitoxin from a mare to her colt. The mare was immunized 25 days after the birth of the colt.

That an active immunity against tuberculosis may be established in cattle has been proven by Pearson and Gilliland,<sup>10</sup> von Behring, Theobald Smith<sup>11</sup> and others.

As early as 1903 von Behring<sup>12, 13</sup> suggested the possibility of conferring upon infants a passive immunity against tuberculosis by feeding them on the milk of vaccinated cows.

I have not been able to find in the literature the report of any experiments which seem adequate to decide this question. In a personal communication dated February 3, 1908, from Dr. Leonard Pearson to Dr. J. H. Knox, Jr., which was kindly placed in my hands by Dr. Knox, I find the following statements:

Von Behring has claimed that the milk of cows immunized to tuberculosis carries immune bodies which are absorbed without change by those fed upon such milk, with the result that resistance to tuberculosis is increased. I do not know of any experiments on a sufficiently large scale to throw important light on this subject. So far as I am aware, von Behring has not published the experiments upon which his conclusion is based.

We have made at the laboratory of the State Livestock Sanitary Board a few experiments, which consisted in feeding a set of swine on the milk of immunized cows and another set of swine on the milk of untreated cows. Subsequently both sets of swine were exposed equally to tuberculosis by feeding cultures. The exposure, as measured by its effects, was rather slight, but still there was a difference in the two sets of swine as shown by post-mortem examination. In one lot there were lesions of tuberculosis in the mesenteric lymphatic glands, while no lesions were found in the swine that had received the milk of immune cows. We have intended for some time to repeat this experiment, but have not yet been able to do so.

In view of the importance of the question the experiments which form the basis of this report were undertaken.

*Object.*—To determine if calves can be immunized against tuberculosis by feeding the milk of vaccinated cows.

*Method to be Employed.*—Six calves of approximately the same age, weight and breed to be selected from healthy, non-vaccinated cows. Three of these calves to be fed from birth with the fresh mixed milk of several vaccinated cows. The three remaining calves to be fed during the same period with an equal amount of fresh mixed milk from non-vaccinated cows, proven by the tuberculin test to be free from tuberculosis. At the end of several months all six calves to be inoculated with a medium dose, lethal for normal calves, of bovine tubercle bacilli. The feeding of all calves to be continued as previously until the termination of the experiment. At the conclusion of the experiment all calves to be autopsied and the lesions present compared.

The general plan of procedure outlined above was followed in two separate series of experiments. The second series was undertaken after the completion of the first and with certain modifications that will be indicated.

*Selection of Calves.*—The calves used in any one series of experiments were of the same breed, within a few days of the same age and, at the beginning of the experiment, were of approximately the same weight. It was, of course, necessary to exclude, as far as possible, the use of calves already infected with tuberculosis. To accomplish this the calves were obtained from a herd in which no tuberculosis was known to exist and their dams were tuberculin-tested shortly after the calves were dropped. In no case was a positive reaction obtained.

*The Vaccinated Cows.*—The vaccinated cows furnishing milk for the first series of calves were immunized as heifers about 18 months before the feeding experiments were started. Their treatment consisted in four intravenous injections of a suspension of living tubercle bacilli of the human type. The suspension used was made in a salt solution, was freed from clumps by centrifugalization and was approximately of the density of a 24-hour broth culture of *B. typhosus*. The first dose consisted of 1 cc. of this suspension; the second dose of 2.5 cc.; the third dose of 4 cc. and the fourth dose of 6 cc. The interval between doses was about three weeks. For the second series of experiments an attempt was made to hyperimmunize the vaccinated cows; a series of ten vaccinations was given, beginning March 7, 1909, and ending May 12, 1910. Injections were made intravenously and consisted of a suspension of tubercle bacilli of human type, prepared as in the preceding series. The dose was gradually increased from 1 cc. at the first injection to 5 cc. at the last injection. The feeding experiments with the milk of these cows were begun ten months after the vaccinations were completed.

*Examination of Milk of Vaccinated Cows for the Presence of Tubercle Bacilli.*—An examination was made to determine if any of the vaccinated cows were shedding tubercle bacilli in their milk at the time these experiments were started. Microscopic examination of the sediment obtained after prolonged centrifugalization at high speed and guinea-pig inoculations of both cream and sediment from the milk failed to reveal the presence of tubercle bacilli.

*Non-Vaccinated Cows.*—The non-vaccinated cows furnish-



ing milk for these experiments were healthy animals, shown to be free from tuberculosis by the tuberculin test.

*Feeding and Care of Calves.*—The calves were nourished by their mothers during the first few days of life until the number requisite to complete the series could be obtained. A new pasture was enclosed by a double fence, a space of about 15 feet being left between the two fences. A double fence divided the pasture into two equal parts, separated by about 15 feet. A new barn was erected on each half of the pasture for the protection of the calves. The group of calves which was to receive the milk from the vaccinated cows was placed in one of these pastures and the group which was to receive the milk of non-vaccinated cows was placed in the other pasture. The two groups of calves were thus kept separated from each other and from contact with any other animals on the farm throughout the experiment. Both sets of calves were fed exclusively on milk during the first few weeks, but later it was necessary to supplement the milk feeding with hay and grain.

*Test Inoculation of the Calves.*—A virulent strain of bovine tubercle bacilli was used for the test inoculation. A suspension of this was prepared by thorough grinding in salt solution. The larger clumps were removed by centrifugalization and the resulting suspension was shown by microscopic examination not to contain aggregates of more than three or four bacilli. This was then diluted with salt solution until it was approximately of the density of a 24-hour broth culture of *B. typhosus*.

The first series of calves received 1 cc. of such a suspension into the anterior jugular vein as a test inoculation. The second series was tested with a subcutaneous injection of 1 cc. of such a suspension behind the right scapula.

#### FIRST SERIES OF EXPERIMENTS.

(This series was started on May 21, 1909.) Six calves were obtained at birth from healthy cows, proven to be free from tuberculosis by the tuberculin test, which was given after the cows had dropped their calves. The calves were divided into two groups of three each, as nearly equal as possible as regards weight and general condition. They were placed in separate pastures and kept thus separated throughout the experiment. To one group was fed the mixed milk of several immunized cows. To the other group was fed the milk of non-immunized healthy cows. The feeding was continued until October 4, 1909, at which time all six calves received intravenously 1 cc. of a suspension of virulent bovine tubercle bacilli. The feeding was continued as previously until the conclusion of the experiment. Following the test inoculation the calves rapidly developed the infection, with loss of weight, roughening of the coats and cough. All six calves died in the fourth week after inoculation. At autopsy the lesions were practically identical in every case. It is therefore unnecessary to give in detail the autopsy findings. Briefly, all showed massive tuberculous pneumonia. The only other macroscopic lesion consisted of an eruption of sub-endothelial tubercles in the right side of the heart. Microscopically miliary tubercles were found throughout the other organs of the body, the spleen,

liver, kidneys and lymph glands. It is evident from this result that the infecting dose was excessive and masked any difference in immunity which may have been present in the two sets of calves. The autopsy findings in these cases are of interest in indicating the fate of the injected bacilli. Although the suspension was practically free from clumps, and any which it may have contained were probably much smaller than a red blood cell, it seems likely that all of the bacilli were arrested in the lungs except those which found lodgment in the right side of the heart and produced the sub-endothelial tubercles present in this situation. The microscopic findings, in the tubercles present in the other organs, indicated that they were formed at a later date and probably resulted from the discharge of bacilli into the systemic circulation, due to the erosion of the pulmonary veins by the lesions in the lungs. A probable explanation for the failure of the injected bacilli to pass through the pulmonary circulation is that they were agglutinated on being introduced into the blood stream. In this connection some experiments from the Bureau of Animal Industry are of interest. A fine suspension of lamp black, the individual particles of which were much smaller than red blood cells, was prepared and injected intravenously into rabbits and a horse. Death followed the injection of comparatively small quantities of this suspension and autopsy showed that all the lamp black had been filtered out in the lungs. It seems not improbable that this result was also due to the agglutinating action of the blood on the particles of lamp black.

Examinations were made to determine if the blood of the vaccinated cows used in this experiment contained any excess of antibodies over the blood of the non-vaccinated cows from which the control calves were fed. Tests were made for agglutinins, precipitins and complement-binding bodies. Agglutinins were present in the serum of some of the members of both groups of cows, but were not present to any greater degree in the vaccinated animals. Precipitins and complement-binding bodies could not be demonstrated in the blood of any of the cows, although various antigens were employed, bacillary suspensions, extracts and tuberculins. In a similar way the blood of the two sets of calves was tested before inoculation and no difference could be determined between the agglutinating, precipitating and complement-binding action of the two groups.

On account of the failure of the first experiment, a second series was undertaken with slight modification.

#### SECOND SERIES OF EXPERIMENTS.

Six calves were obtained from healthy cows, shown to be free from tuberculosis by the tuberculin test, applied within a few days after the calves were born. These calves were divided into two equal groups. New, separate pastures and barns were prepared for them as in the preceding series and they were kept separated throughout the experiment. Feeding was begun on March 9, 1911. One group received milk from the hyperimmunized, the other group from non-vaccinated, healthy cows. On December 1, 1911, all six calves received the same dose of virulent bovine tubercle bacilli, 1 cc.



of the suspension subcutaneously, behind the right scapula. The feeding was continued as previously until the experiment was terminated. The calves receiving milk from immunized cows thrived better than the other group and at the time of autopsy weighed about 25 per cent more than the controls. It is unfortunate that the three calves receiving milk from immunized cows were all bulls while the other three calves were heifers. This fact may account in part for the difference in the general condition at the conclusion of the experiment. A month or six weeks after inoculation it became evident that local lesions had been produced in all three of the calves receiving milk from the non-vaccinated cows. In one of these the lesion broke down and left a discharging sore. Subsequently these three calves showed clinical evidence of infection which consisted in roughening of the coats and retarded development. The three calves which received milk from vaccinated cows likewise developed local lesions, but careful palpation was necessary in order to reveal them.

One calf from each group was killed and autopsied on March 16, 1912. The autopsy showed as follows: The calf which had received milk from immunized cows showed a small lesion at the site of inoculation, about 2 cm. in diameter, containing caseous material and surrounded by a thick fibrous wall. The related axillary lymph glands showed small caseous nodules and there were a few caseous areas in the bronchial lymph glands. The control animal showed at the site of inoculation a caseous abscess, 6 to 8 cm. in diameter, with a thin wall. The related axillary lymph glands were enlarged and caseous, as were also the bronchial lymph glands and those in the region of the gall-bladder. The liver contained 15 to 20 caseous areas 1 to 5 cm. in diameter.

The microscopic examination of tissues from the calf which had received milk from immunized cows showed the tonsil, lung, heart, spleen, kidney (2 sections), adrenal and testis to be normal. The abscess wall at the site of inoculation showed a dense fibrous wall, 1 mm. thick, lined with a layer of very vascular tubercular granulation tissue. A section of one lymph gland showed two healed tubercular lesions, 2 mm. in diameter, and about the periphery smaller tubercles of more recent origin. The calf receiving milk from non-immunized cows showed at the site of inoculation a fibrous wall about the same thickness as the above, the granulation tissue lining it being less vascular and containing fewer giant cells than in the preceding case. The tissue surrounding the abscess, consisting of connective tissue, fat and voluntary muscle, showed a very acute inflammatory process containing fibrin and polymorphonuclear leucocytes with recent tubercles scattered throughout. Evidently a mixed infection had been present. Two lymph glands were examined; one showed a small tubercle; the sinuses of the other showed numerous giant cells without any definite tubercle formation. The liver showed numerous conglomerate tubercles of both the proliferative and exudative type. The spleen showed well-marked conglomerate tubercles of the proliferative type. Sections from the lung, heart, kidney and ovary were negative.

A second pair of calves was killed and autopsied on Decem-

ber 13, 1912. The one that had received milk from vaccinated cows showed at the site of inoculation a tuberculous lesion, 3 to 4 cm. in diameter, with a thick fibrous wall. The retropharyngeal lymph glands were about 3 cm. in diameter and contained a few small tubercles. The liver contained four nodules, 1 to 3 cm. in diameter. The control animal showed at the site of inoculation a tuberculous abscess, 10 to 12 cm. in diameter, which had infiltrated the surrounding tissue. The axillary and prescapular lymph glands on both sides were tuberculous, as were also the retropharyngeal and bronchial lymph glands. Scattered throughout both lungs were areas of tuberculosis which measured up to 1 cm. in diameter. The liver contained a number of caseous areas from 1 to 5 cm. in diameter.

The microscopic examination of tissues from the calf which had received milk from immunized cows showed the lung, heart, kidney, a hemolymph node and a section from one of the serous glands free from tuberculosis. The report on sections from the lymph glands examined was in seven instances negative for tuberculosis; in two instances "no definite tuberculosis"; and in one case "a few healed tubercles (?)." The liver showed numerous miliary and conglomerate tubercles; in places extensive caseation and calcification. The spleen showed small scattered areas containing small round hyalin masses and epithelial cells (venous thrombi); no caseation, no giant cells. The abscess wall at the site of inoculation showed scar tissue, containing some caseous and calcified areas. Microscopic examination of tissues from the control calf for the preceding, which had been fed the milk of non-immunized cows, showed at the site of inoculation a very thin layer of scar tissue enclosing tuberculous granulation tissue and caseous material. A section consisting of connective tissue, fat and voluntary muscle from outside the abscess wall showed a large mass of tuberculous tissue with areas of caseation and calcification. Sections from four lymph glands examined showed extensive tuberculosis. Section from the lung showed an encapsulated tubercular mass with a few small proliferative tubercles scattered elsewhere. The liver showed tuberculosis and the spleen showed small recent miliary tubercles. Other organs examined were negative for tuberculosis.

The two remaining calves were killed and autopsied on December 16, 1912. The one which had fed upon milk from the vaccinated cows showed at the site of inoculation a tuberculous abscess, approximately 3 by 6 cm., surrounded by a thick fibrous wall. No other macroscopic lesions were discovered except four nodules in the liver, which varied from 1 to 3 cm. in diameter. The control animal showed minute caseous areas in the retropharyngeal and bronchial lymph glands, and scattered throughout both lungs were numerous areas of tuberculosis measuring up to 1 cm. in diameter.

Microscopic examination of the tissues from the calf which had received milk from immunized cows showed the lung, heart, liver and testis free from tuberculosis. Of the sections from 12 lymph glands examined, 9 were free from tuberculosis. Two showed a few small, indefinite tubercles and one showed extensive tuberculosis. The report on the spleen was, "Small



recent, indefinite tubercles (?)." The abscess wall consisted of fibrous and tubercular tissue containing caseous and calcareous material. Microscopic examination of the tissues from the control calf for the preceding, which had received milk from non-immunized cows, showed tuberculosis in a section removed from the site of inoculation, containing striated muscle and lymphoid tissue. Of 13 lymph glands examined microscopically, 4 showed tuberculosis. The liver contained numerous conglomerate tubercles. The spleen contained small scattered tubercles. A section from the heart and two sections from the lungs showed no tuberculosis.

As in the preceding series, the blood of the two sets of cows furnishing the milk for these experiments was tested for tuberculo-antibodies. No difference could be determined by means of the agglutinin, precipitin and complement-binding tests. Nor did similar tests show any difference between the blood of the two sets of calves.

The result of the second series seems to justify the conclusion that a relative degree of immunity against tuberculosis may be conferred upon calves by feeding the milk of vaccinated cows. Further experiments are necessary to determine if human beings may be similarly influenced.

The experiments reported above were suggested to me by Mr. S. M. Shoemaker, of Eccleston, Md. It is a pleasure to acknowledge my indebtedness to Mr. Shoemaker, not only for his generosity in defraying all the expenses of the work, but also for many valuable suggestions in the actual conduct of the experiments.

I am also indebted to Dr. S. H. Gilliland, of Marietta, Pa., who performed all of the vaccinations on the cows used in these experiments, as well as all of the tuberculin tests. He also prepared the suspensions of virulent bovine tubercle bacilli and gave the test inoculations to the calves.

For the microscopic examination of the tissues removed at autopsy, I am indebted to Dr. Thos. P. Sprunt, of Baltimore.

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## COMPLEMENT FIXATION IN THYROID DISEASES.<sup>1</sup>

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Perhaps no field of research has been more vigorously worked in recent years than that which deals with the subject of *functional diagnosis*. With an ever-increasing knowledge of the physiology of the various glandular organs of the body and a wider recognition of the part which they play in various diseases, attempts have been made to devise clinical tests which would give accurate information as to the extent to which any given gland was performing its normal duties. Numerous examples might be mentioned, such as the desmoid test of Sahli, Strauss' levulose tolerance test for hepatic insufficiency, Schmidt's nuclei test for pancreatic activity, and finally the well-known phenol-sulphon-phthalein test of Rowntree and Geraghty which, as applied to the diagnosis of renal conditions,

probably represents to-day the best and most highly specific of all laboratory functional diagnostic methods. It is not at all surprising, in view of the growing interest in the endocrine glands, that attempts have been made to discover methods for the recognition of normal and abnormal activity in them. The problem here, however, is obviously a much more complex one than that which deals with glands possessing ducts, for the endocrine glands are so intimately connected one with the other, either through the agency of the central nervous system or through the action of their specific hormones, that it is extremely difficult, while attempting to study the function of any one particular gland of internal secretion, to eliminate the influence of all the others.

Probably by reason of the frequency with which disorders of the thyroid gland occur, the most vigorous studies have

<sup>1</sup> Reported before The Johns Hopkins Hospital Medical Society, Dec. 7, 1914.



been put forth toward understanding the functioning of this gland in health and disease, and particularly because, although the clinical manifestations of dysthyreosis are in so many instances easy to recognize, in another large group the evidence is often tangibly inconclusive, despite the fact that suspicion may amount almost to certainty in the mind of the observer. All the other endocrine glands as well have been studied with great care and methods devised which, though still imperfect, are very helpful in arriving at a diagnosis when taken in conjunction with careful clinical and experimental studies. Writing in the early part of 1914, Dr. Barker<sup>1</sup> called attention to the fact that there existed at that time four so-called functional tests for thyroid activity which, though usually positive in outspoken cases of Graves' disease, are almost always negative in the milder types, the so-called *formes frustes*. Brief reference to these four tests may be of interest.

1. *The Acetonitrile Test* of Reid Hunt<sup>2</sup> first described in 1905. In a series of well-controlled experiments Hunt was able to demonstrate that white mice fed on thyroid extract in the form of Ehrlich cakes became much more resistant to the toxic effects of hypodermic injections of acetonitrile, a drug which is poisonous by reason of its slow liberation within the body of hydrocyanic acid. If the animals were first fed on the blood of thyroidectomized animals, they failed to show this increased drug resistance. In a large series Hunt noted no such resistance to other drugs which were tried, morphine excepted. Trendelenburg<sup>3</sup>, in 1910, was able to confirm Hunt's findings, and further amplified them by showing that white mice fed on blood taken from patients suffering from Graves' disease also became more resistant to the injection of the drug. Ghedini,<sup>4</sup> in reviewing the work in 1911, was not only able to demonstrate the truth of Hunt's observations, but also noticed that a similar increased resistance followed the feeding of blood-serum taken from patients suffering from chronic nephritis and a number of other conditions which were not in any way apparently associated with thyroid hyperactivity.

2. *The Demonstration of Hyperadrenalinemia*.—Though numerous chemical methods had been introduced to detect quantitatively the presence of adrenalin in the circulating blood, it remained for Fraenkel<sup>5</sup> to demonstrate, in 1909, an increase in this substance in the blood of patients suffering from exophthalmic goiter. His test consisted in comparative observations upon the strength and frequency of contractions of isolated rings of the excised uterus of rabbits when immersed in oxygenated Ringer's solution, human serum and adrenalin solutions. Since then a number of other methods, all of a biological type, have been employed to demonstrate an increase of adrenalin in the blood. Of these the following may be mentioned:

(a) The test of Melzer and Ehrmann,<sup>6</sup> which is based upon the production of mydriasis when adrenalin is instilled into the enucleated eye of a frog.

(b) Cameron,<sup>7</sup> as the result of her investigations, concludes that the best method for testing the blood concentration of adrenalin is by determining the effect upon the blood pressure of rabbits which have been previously atropinized.

(c) Hoskins<sup>8</sup> has devised a method based upon the fact that adrenalin inhibits the movements of the isolated loop of a rabbit's intestines in oxygenated Ringer's solution.

(d) Based upon the fact that adrenalin constricts a strip of peripheral artery and causes relaxation in a strip of the coronary artery, Janeway and Park<sup>9</sup> have devised a method by means of which one part of adrenalin in 50,000,000 parts of Locke's solution or in 20,000,000 parts of blood may be detected.

All these biological methods doubtless demonstrate the presence of an increased adrenalin content, nevertheless they are hypersensitive, not particularly easy to carry out as routine clinical tests and, moreover, they vary tremendously when applied to various normal individuals. Falta<sup>10</sup> even doubts whether these reactions are specific for adrenalin at all. Though it has been shown that the intravenous injection of thyroid substance does produce an increased adrenalinemia, it has not been shown that an increased adrenalin content is a constant feature of Graves' disease, while, on the other hand, such an increase has been found in a number of other states, notably states of emotion, especially of fear, a point brought out more particularly by the researches of Cannon.<sup>11</sup> With reference to these first two functional tests mentioned, Eppinger<sup>12</sup> states that, although they are of considerable scientific interest, they as yet possess no definite clinical value.

3. *Abderhalden's Dialysis Test*.—Since the publication, in 1912, of Abderhalden's<sup>13</sup> dialysis method for the demonstration of protective ferments in the blood, the test with its underlying principles has been applied to almost every conceivable condition. The results thus far have been discordant in the hands of many observers, and the exact clinical and scientific status of the test still remains an undetermined factor. Lampé and Fuchs<sup>14</sup> have used the test quite extensively in the study of Graves' disease and other thyroid conditions. From their studies of some sixty cases, they arrived at the following conclusions:

(a) The serum from a case of Graves' disease splits a substratum of Basedow thyroid tissue consistently, and occasionally may split normal thyroid tissue as well.

(b) The same serum is generally capable of splitting substrata prepared from the thymus and sex glands.

(c) Practically the same results are observed in "Basedowoid cases" or cases of simple hyperthyroidism.

(d) Sera from cases of myxœdema and endemic goiter are also capable of splitting thyroid tissue.

From these findings they came to the opinion that in Graves' disease there is both a hyper- as well as a dys-functioning of the thyroid and of the sex glands as well, and that in myxœdema and endemic goiter also, there is present a dysthyreosis, but one of a different type, the nature of which is still obscure. Up to the present time their work has not been confirmed, and the clinical value of the entire Abderhalden technique, more particularly as regards its specificity as an indication of the dys-functioning of the thyroid or of any other organ, is as yet undecided.

4. *Roseo's<sup>15</sup> Complement Fixation Test*.—The application of Roseo's name to this particular test is apparently unwar-



ranted, for in an article by Papazolu,<sup>16</sup> written in 1911 on the same topic, reference is made to complement fixation tests performed in 1908 by Marinesco. Apparently his work was not published, but was continued by his pupil, Papazolu, who in 1911, by using etherial extracts of thyroid tissue removed at operation, obtained complement fixation with the sera of 26 out of 38 cases of Graves' disease; the same sera gave no fixation with antigens prepared from normal thyroid or parenchymatous goiter. In another monograph referred to by Klose,<sup>17</sup> the same author reports positive reactions in 58 out of 60 cases of Graves' disease. He further noted that some luetic sera, used as controls, bound complement in the presence of the etherial extract of normal thyroid tissue; and he came to the conclusion that in exophthalmic goiter the dysfunctioning gland acts as an antigen and causes the production of antibodies demonstrable by the Bordet-Gengou phenomenon. In 1913 Roseo reported the results secured by using the aqueous extracts of two Basedowian thyroids, the work being a continuation of some earlier observations of his upon this same reaction. He reports positive results with both antigens in four out of five cases of classical Graves' disease. Of these cases, however, two gave a positive Wassermann reaction, though five known luetic sera were negative as tested with both thyroid antigens. No details of the methods of control for these tests are given. Both Papazolu and Roseo agree in stating that the reaction is negative in the abortive forms.

Numerous other studies have been made upon the bio-chemistry of Basedowian blood. Kottman<sup>18</sup> and Lidsky and others have found that the coagulation time is increased, and that this change can be induced by injections of potassium iodide or of thyroid substances, an observation confirmed in Klose's clinic. The reverse condition has been observed in myxoedema, and hence this test is considered of some differential diagnostic value. Since the thyroid secretion increases the metabolism of the body, the blood contains an excess of protein-split products and hence the freezing point of the blood is lowered, a fact also observed by Klose. Hyperglycemia has been observed quite constantly in Graves' disease and by many is explained by the increased adrenalin content. Wälli<sup>19</sup> has found a constant increase in the anti-trypsin content of the blood in cases of Graves' disease, this increase being manifested even in the earliest stages and long before the cardinal symptoms are prominent. The index varies directly with the stage of the disease.

Of the four functional tests referred to by Dr. Barker, the last one seemed the most likely to yield conclusive results and the present report deals with a study of its value.

#### METHODS AND MATERIALS EMPLOYED.

(A) *Antigens*.—All of the antigens used were prepared from thyroid tissue which was secured at the time of operation from patients suffering with outspoken Graves' disease. That such was the case was always confirmed by a careful analysis of the patient's clinical history, subjective and objective findings, and parallel observations upon the histology of the tissues in question. The thyroid tissues were secured through the

kindness of Dr. Halsted and Dr. Finney of this clinic, and through the hearty cooperation of Dr. E. F. Butler of the Mayo Clinic, and of W. J. Rogers of Dr. Crile's service at Lakeside Hospital, Cleveland. To all of these we express our thanks for the specimens and records furnished us.

As soon after removal as possible the tissues were weighed and, where possible, were divided into two or more portions, so that from one and the same gland two or three different types of antigen could be prepared. The specimens received from Cleveland and Rochester were in sealed, sterilized containers, and showed no evidence of autolysis at the time that they were received. In general the tissue extracts or antigens were made up in proportions similar to the original formula used by Wassermann in the reaction which bears his name. In other instances the tissues were extracted with 2, 5 or 10 volumes of the fluids used. The various types of antigens thus prepared were of the following nature:

(a) Aqueous: Made up with sterile, normal saline and preserved by the addition of suitable small amounts of tricresol.

(b) Alcoholic: 95 per cent and absolute alcohol were both employed.

(c) Acetone.

(d) Extracts obtained with equal parts of alcohol and ether.

(e) Aqueous and alcoholic extracts sensitized by the addition of Bayer's iodothylin.

(f) Alcoholic extracts strengthened by the addition of .1 per cent iodine.

In most instances the antigens were prepared by a preliminary shaking process followed by incubation for from one week to ten days at 37° C. Prior to the use of any antigen it was carefully tested in the usual manner for the following points: (1) Whether it was capable of producing hemolysis alone; (2) whether it was anticomplementary, and if so, in what dilution; and (3) whether it was capable of fixing complement in the presence of a normal serum.

(B) *Sera*.—The sera to be tested were all secured either by the usual method of venous puncture or were obtained at the time of operation directly from one of the thyroid arteries. After centrifugalization, the sera were inactivated at 56° C. for half an hour and diluted 1-5 with normal salt solution, after which they were tested in the following ways:

(a) Wassermann examinations were made, each serum being tested against three different antigens of the following nature, namely, an alcoholic extract of luetic liver; an alcoholic extract of human heart; and, finally, a similar extract sensitized with .4 per cent cholesterol.

(b) Every serum was tested against each of the thyroid antigens, 19 in all, each antigen being in five different dilutions, namely, 1-5, 1-10, 1-20, 1-30, and 1-40. In cases where spinal fluids were employed, no inactivation nor dilution of the fluid was resorted to. Throughout the work complete hemolysis was represented by a cipher, complete fixation or inhibition of hemolysis by the figure 4; the unit of volume chosen was .2 cc. Complement was secured from the guinea-pig, and an anti-sheep amboceptor of high hemolytic titre was employed. Suitable amboceptor and complement titra-



tions were run preliminary to each series of thyroid-fixation tests.

RESULTS.

The cases which have been submitted to tests against the thyroid antigens above described fall into six definite groups:

(a) Cases of true Graves' disease. The blood for these cases was always secured prior to operation. This group includes cases also of acute exophthalmic goiter, a typical history of one of which is as follows:

K. H., male, aged 38, was admitted, complaining of nervousness. He presented a remarkable family history in that his mother had had simple goiter for many years, his eldest sister had been operated upon for Graves' disease, and his eldest daughter was suffering from the same malady. In good health

(e) Sera from a group of patients known to be syphilitic. All of these sera gave complete fixation with the Wassermann reaction and were secured from patients in all stages of the disease.

(f) Spinal fluids employed in the present study were all taken from undoubted cases of general paresis.

The results of the complement fixation reaction in the present study are clearly shown in Table I. An examination of this table shows that the results have been *consistently negative in all except the luetic cases*. In other words, there has been no evidence of complement fixation except in the case of those sera or spinal fluids which were known to have had and were proved to have a positive 100 per cent Wassermann reaction. This fact affords further evidence of interest with reference to

TABLE I.  
SHOWING THE NUMBER OF COMPLETE FIXATIONS GIVEN BY EACH OF 19 DIFFERENT THYROID ANTIGENS AS TESTED AGAINST 58 CASES OF VARIOUS TYPES.

Types of Antigens.		Aqueous Antigens.							Alcoholic Antigens.					Alcoholic extract plus .1% iodine.	Alcoholic extract No. 99597 plus iodothylin.	Alcoholic ether extract. Equal parts No. 46677.	Acetone Antigens.			Positive Wassermann in blood or spinal fluid of the cases examined.
Number of cases.	Type of cases.	93663.	99597-A.	100245.	Calep.	Smith.	46371.	99758.	47039.	99736.	99597-B.	93663-A.	99647.				93663-B.	67882.	99846.	
2	Acute Graves' disease.....	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7	Exophthalmic goiter .....	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
4	Hyperthyroidism.....	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
1	Simple goiter.....	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
6	Unexplained tachycardia.....	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
10	Dementia præcox.....	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
22	Luetic sera.....	0	0	0	2	2	0	0	0	21	21	20	21	0	0	20	22	22	22	22
6	Paretic spinal fluids.....	0	0	0	3	3	0	0	0	6	6	6	6	0	0	6	6	6	6	6

up until one month previously, he suddenly became nervous, noticed an increase in the size of his neck, was very irritable, had palpitation of the heart, shortness of breath, and his friends noted a bulging of his eyes. His appetite had increased markedly, though his weight had fallen off perceptibly. All of these symptoms had increased up until the time of admission. When he entered the hospital his pulse was 146, his respirations were 22, and the objective findings of exophthalmic goiter were marked in every respect.

(b) Cases not outspokenly exophthalmic in type, but diagnosed clinically as instances of hyperthyroidism.

(c) Cases showing unexplained tachycardia. These were all observed in the Phipps Psychiatric Clinic and in no instance was there any demonstrable involvement of the cardiac muscle. The cases in question fall into scattered clinical groups.

(d) In view of the findings of numerous investigators who have applied the Abderhalden technique to the study of cases of dementia præcox, it seemed worth while to attempt the application of complement fixation methods to a series of such cases.

the non-specificity of the Wassermann reaction and raises some new questions as to the nature of the reacting substances in this valuable test. Only one opportunity was afforded to note how luetic sera would react with an antigen prepared from a normal thyroid, but the evidence, as based upon the testing of some ten or twelve positive sera against it, was all on the negative side; that is, no fixation was secured. The weight of evidence at present is in favor of the view that the Wassermann reaction is essentially one in which the lipid bodies are particularly concerned. As yet no observations upon the lipid content of the Basedowian thyroid have been found in a search through the literature. It is of interest in passing to call attention to the fact that unsaturated fatty acids are important in the Wassermann reaction, for it is known that the antigen value of the acetone insoluble fraction of the tissue lipoids varies, according to Noguchi and Bronfenbrenner,<sup>20</sup> almost directly with its power to combine with iodine.

The idea that complement-fixation methods might be of value in thyroid and other glandular conditions is to be found in certain works published by Stephan and Oeller<sup>21</sup> upon the



value of the Abderhalden reaction. These authors were able to show that, if a serum capable of splitting a given substratum is first inactivated, it is thereby rendered inert, but that it may be made to refraction by the addition of guinea-pig's serum, in other words, complement. As a result of their experiments, they came to the conclusion that ferments in the sense that Abderhalden uses the word, do not exist as such, but are nothing more than amboceptors in the sense in which Ehrlich first introduced this term. They were inclined to believe that the method of complement fixation could be used for the demonstration of antigen-antibody reactions of many kinds, and in fact were able to apply this method successfully in the diagnosis of pregnancy. They believe that the human body is, in states of disease, autosensitized with the products of abnormal intermediate metabolism, or with the perverted secretions of one or more of the endocrine glands, and that war is constantly being waged upon the endogenous toxins thus produced. In response to each autosensitizing abnormal product or antigen, specific antibodies are produced, which are rendered inert by their fixation with the patient's own complement. Assuming that this were the case, suitable methods of the application of the Bordet phenomenon should be capable of revealing which organ or gland in the body is responsible for the symptoms which clinically are referred to it.

The results here reported are at marked variance with those of Roseo and Papazolu; Roseo's paper is singularly meager in the description of the technique employed and his results are based upon a very small series. With reference to Papazolu's positive findings, it should be noted that he employed etherial extracts as antigens; just how these were made to mix with the other components of the test is not stated—nor how evaporation was prevented during incubations. Though the series here reported is not large, the cases chosen are all of a classical

type; and it is felt that the testing of each serum against so many different antigens is more than equivalent to a larger number of sera tested with but one or two extracts of the same nature.

The method as employed here with suitable controls has been singularly unproductive and we are therefore of the opinion that the complement fixation test of Roseo is of absolutely no value as a clinical measure in determining the existence of hyperthyroid states or conditions of dysthyreosis.

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TWO PHYSICIAN-ECONOMISTS.<sup>1</sup>

SIR WILLIAM PETTY, 1623-1687; FRANÇOIS QUESNAY, 1694-1774.

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[NOTE.—The authoritative biography of Petty is Lord Edmond Fitzmaurice's "The Life of Sir William Petty, 1623-1687, chiefly derived from private documents hitherto unpublished" (London, 1895). Professor Charles H. Hull's definitive edition of "The Economic Writings of Sir William Petty, together with the Observation upon the Bills of Mortality, more probably by Captain John Graunt" (Cambridge, 1899), contains a wealth of biographical and bibliographical detail, as well as a convincing determination of the Petty-Graunt controversy, and a complete bibliography of Petty's published writings (pp. 633-660).

Quesnay's life and work can best be approached through Georges Weulersse, "Le Mouvement Physiocratique en France" (Paris, 1910), and thereafter studied at first hand in Auguste Oncken's "Oeuvres Economiques et Philosophiques de F. Quesnay, fondateur du système physiocratique, accompagnées des éloges et d'autres

travaux biographiques sur Quesnay par différents auteurs" (Francfort et Paris, 1888). Brief but excellent outlines of Quesnay are contained in Lavergne, "Les économistes français du dix-huitième siècle" (Paris, 1870) and in Higgs, "The Physiocrats" (London, 1897). An annotated bibliography of Quesnay's writings is included in Oncken, pp. 809-814.

In connection with the reading of the present paper, there were shown the original editions of Petty's notable economic works from the writer's collection, and also the more important of Quesnay's medical works from the library of the Surgeon-General's Office. The mezzotint portrait of Petty by Smith after Closterman's painting, and Will's line engraving of Quesnay after Chevalier's portrait, were also exhibited.]

The interrelation of social philosophy and medical science is a commonplace of current thought. This connection is three-fold in kind: a parallelism in scope, an association in

<sup>1</sup> A paper read before the Historical Club of The Johns Hopkins Hospital on March 8, 1915.



content, and a contact in doctrinal history. The writings of Darwin, Spencer, and Huxley have made such terms as "social organism" and "economic evolution" familiar phrases in economic composition. There is, indeed, no radical novelty in this mode of expression. From Aristotle's description of man as a political animal, the curious will find a recurrent anticipation of "the biological analogy" in socio-economic literature.

Not only is the social body comparable in structure and in function to the human body, but the disorders of society are analogous to the diseases of man. There is thus a social pathology with its implications of social diagnosis, social prognosis and preventive social treatment. It is astonishing how early and with what clearness this parallelism was set forth. More than three hundred years ago an earnest economic writer, Gerard De Malynes, making inquiry into "the canker of the commonwealth," declared upon the title page of his tract that, "the Author imitating the rule of good Phisitions, First, declareth the disease. Secondarily, sheweth the efficient cause thereof. Lastly, a remedy for the same."<sup>2</sup>

More important than the analogy in scope is the intimate association in content, of economics and medicine. The standard of living, the principle of population, the dependence of industrial efficiency upon food and working hours—suggest the recourse of social philosophy to medical science. On the other hand, occupational disease, the less spectacular but more tragic ravages traceable to insufficient wage income, the possibilities of public expenditure in the prevention of disease—point to the necessary reliance of the physician upon economic philosophy. Indeed, the neglect of this kinship has, on more than one occasion, proved hurtful. The economist would have qualified his generalization as to the necessary level of a socially desirable wage by fuller acquaintance with modern dietetics in relation to the nutritive quality of food materials. The physician would have been more guarded in his advocacy of the sanitarium as the essential weapon in the social campaign against tuberculosis had he made more intimate study of the amount and regularity of the workingman's income.

Tempting, however, as are such matters of parallelism and interrelation, it is exclusively with the third of the connections noted between economics and medicine—the contacts in doctrinal history—that I propose briefly to engage your attention. By "contacts," I mean not the mutual indebtedness of economic doctrines and medical theories, a phenomenon already referred to as "association in content," but rather the circumstance that there have been, from time to time, individuals who have attained distinction both as political economists and as physicians, and whose contributions in each field—bearing in mind the essential unity of intellectual effort—may be conceived as influencing the contributions in the other.

It would be an inviting task to attempt a reasonably complete catalogue of such physician-economists. We should think of John Locke, philosopher and statesman—the friend of

Sydenham and the physician of Shaftesbury—whose contributions to medical practice were generously appraised by Sir William Osler at the celebration of the bicentenary anniversary of Locke's death held at this University ten years ago;<sup>3</sup> but whose notable services to economic science in establishing the foundations of modern monetary theory in the famous re-coinage discussion of 1690-96 and in laying the basis of modern theories of private property and economic value, were curiously omitted.

There would be Nicholas Barbon—the son of Praisegod Barebone—student of Leyden, graduate of Utrecht, and honorary fellow of the College of Physicians. Instrumental in establishing the first fire insurance office in London, a member of Parliament, active in re-building the city after the great fire, and a projector of the short-lived national land bank that paved the way for the Bank of England in 1694, Barbon found time to write notable tracts on trade and currency whose ingenuity Bauer regards as memorable in "der Vorgeschichte der klassischen Oekonomie"—before dying in 1698, having appointed John Asgill, the economist, to be the executor of his will, and having directed that none of his debts should be paid.<sup>4</sup>

We should give a place to Bishop Berkeley—theologian, philosopher, idealist—author on the one hand of "The Querist," perhaps the most thoughtful economic composition of the first half of the eighteenth century, and on the other hand, of "Siris," that curious intermixture of "philosophical reflexions" and "inquiries concerning the virtues of tar water"—from which grew the war of pamphlets as to the efficacy or otherwise of this homely specific, which figures at least amusingly in the history of English medicine.<sup>5</sup>

<sup>3</sup> November 1, 1904. No report of the celebration—at which Locke's contributions to philosophy, psychology, toleration, politics and social philosophy were described by distinguished scholars—appears to have been published. Sir William Osler's address on "John Locke as a physician" appeared in the *Lancet*, October 20, 1900, ii, 1115-1123, and was reprinted in "An Alabama Student, and Other Biographical Essays" (Oxford, 1908). Dr. Osler has been kind enough to write me further: "I am much interested in Petty. I picked up his MS. letter book, 1661-84, and at the back found, bound in, the agreement with Fleetwood to do the Down Survey. I gave it to Trinity College, Dublin. I have a very good collection of his original works, including the Survey. He was a remarkable man, one of the most distinguished professors Oxford ever had. It was a great loss to medicine when he got mixed up with Irish affairs."

<sup>4</sup> Barbon's life and economic writings are described by Dr. Stephen Bauer in Conrad's *Jahrbücher für Nationalökonomie und Statistik* (Jena), XXI. Bd. N. F., pp. 561-590; also by the same writer in "Dictionary of Political Economy" (ed. Palgrave), *sub nom.* I have reprinted (Baltimore, 1905), with an introductory word and a few notes Barbon's rare "Discourse of Trade" (1690), the title page of which bears the signature "N. B. M. D." Of Barbon's medical work, nothing is known.

<sup>5</sup> The history of the tar-water controversy is traced and the more important of the tracts evoked thereby is included in Professor Fraser's admirable preface to "Siris" in "The Works of George Berkeley, D. D." (Oxford, 1871), Vol. ii, pp. 343-357. "The Querist" may be found in Mr. George Sampson's excellent three-volume edition of Berkeley's writings (London, 1897-8), or

<sup>2</sup> Gerard De Malynes, "A Treatise of the Canker of Englands Commonwealth" (London, 1601).



So, too, Bernard de Mandeville—a physician and a son of a physician, a student of Rotterdam, a graduate of Leyden in 1689, and a practitioner come upon evil days in London. An early advocate of the Cartesian theory of automatism among animals, a stimulating essayist upon “Hypochondria” and an opponent of speculative therapeutics—Mandeville became famous, or infamous, as the author of “The Fable of the Bees”—an ingenious political satire of the state of England in 1705, whose philosophic half-truths gave Adam Smith the germ of his doctrine of self-interest as the dominant motive of socio-economic action, and perhaps even paved the way for nineteenth century utilitarianism.<sup>6</sup>

Of this goodly company<sup>7</sup> I have selected two worthies for somewhat closer notice—Sir William Petty and François Quesnay. In the history of medicine the position of each is at least respectable. In the history of economics, it is distinguished. Petty, if not, as he has been called,<sup>8</sup> “the founder of political economy”—was the first to insist that economic facts must be studied by the precise methods of physical science, and to that end fashioned the device of “political arithmetic.” Quesnay, the author of the “Tableau Economique”—which the elder Mirabeau grouped with the alphabet and money as the three great inventions of the human mind—was the master of the first real school of political economists, the *économistes* or physiocrats of pre-revolutionary France. Finally, each figured appreciably in the history of his time. Petty was the director of the Down Survey of Ireland, and became the progenitor of the Lansdowne family. Quesnay was the trusted physician of Madame de Pompadour and an influential court figure in the closing decades of the *Ancien Régime*.

The facts of Petty's life, long familiar in essential, have been elaborated in recent years by his lineal descendant, Lord Edmond Fitzmaurice, with the aid of family archives, and it is of this record that liberal use has been made in the following paragraphs.<sup>9</sup> Born at Rumsey, in Hampshire, in 1623, the son of Anthony Petty, of whom Aubrey states that “by profession

more conveniently in the reprint which I have edited (Baltimore, 1910) with the title-pages of the original edition reproduced in facsimile and the original pagination indicated.

<sup>6</sup> Mandeville's economic philosophy is discussed in James Bonar, “Philosophy and Political Economy” (London, 1893), passim, in Leslie Stephen, “History of English Thought in the Eighteenth Century” (second ed., New York, 1881) chap. IX, sect. iii, in Edwin Cannan (ed.), “Adam Smith's Wealth of Nations” (London, 1904), xliii-xlvi and in “Dictionary of Political Economy” (ed. Palgrave), *sub nom.*

<sup>7</sup> I am indebted to Dr. William H. Welch for the happy reminder that mention should at least be made of Copernicus, who, on the one hand, pursued medical studies at Padua and engaged in active practice at Frauenburg, and who, on the other hand, presented a scheme for the reform of the Prussian Polish currency in a treatise, “De monetæ cudendæ ratione,” which Wolowski made accessible in 1864 in conjunction with the currency tract of Nicole Oresme.

<sup>8</sup> Lord Edmond Fitzmaurice in “Dictionary of Political Economy” (ed. Palgrave) *sub* “Petty.”

<sup>9</sup> A sketch of Petty, based upon Fitzmaurice, appeared in the *British Medical Journal*, June 11, 1898, pp. 1529-1531, under the caption, “Lord Lansdowne's Medical Ancestor.”

he was a clothier, and also did dye his own cloths,” Petty received the usual school education, including “a competent smattering” of Latin and Greek, but mitigated by contact in leisure hours with the trades and crafts of the neighborhood. Chafing under home restraint, Petty at fifteen bound himself apprentice to the master of a sailing vessel. The experience was short and painful. He was ill-treated at sea, and finally left stranded with a broken leg at a small inn on the French coast near Caen—perhaps his first grim acquaintance with the opportunities of surgical skill. His plight excited the sympathy of the neighborhood, and his precocity won friends and patrons. Abandoning the sea, he entered a private school, and later the Jesuit College at Caen, the Fathers consenting to take the young Englishman as a pupil with the condition “that their attempts on his religion should be confined to prayers for his conversion.”<sup>10</sup>

After leaving the college at Caen, young Petty entered the Royal Navy; but at the outbreak of the Civil War he retired to the continent, not to return to England until three years later, in 1646. These three *Wanderjahre* were spent in France and in the Netherlands. At Utrecht, Leyden, Amsterdam and later at Paris his interest, converging upon the physical and mathematical sciences, eventually concentrated upon anatomy. In Paris he met Hobbes, and Aubrey records that they read Vesalius together. These were rare days in France. The spirit of scientific inquiry was in the air and the old limits upon human knowledge seemed passed.

Returning to England in 1646, Petty, then twenty-three, was driven less by preference than by lack of other opportunity to recur to his father's business. Other projects engaged his leisure—an invention for double writing, a college of tradesmen, and the design of a history of trade. But an even more ambitious intention was forming. “A most rare and exact anatomist,” wrote Hartlib of Petty to Boyle, and Petty himself records, “I intend, God willing, so soone as possibly I can, to take the degree of Dr. of Physicke,” adding comfortably, “which being done, it will bee a discredit for mee and consequently a great hindrance to mee, to goe and buy small matters, and to doe other triviall businesses.”<sup>11</sup>

Petty enjoyed the friendship of influential supporters of the Protector, and in due course was created a fellow of Brasenose. The appointment was variously justified as made because “of his rare qualities and gifts,” because “he had cut up Dogges and taught anatomy in the war,” and somewhat spitefully, because the visitors “liked to put out loyal persons in order to put him and such others in.” With the fellowship came appointment as Deputy to the University Professor of Anatomy, Dr. Clayton—whose efficiency was apparently impaired by “an insurmountable aversion to the sight of a mangled corpse.” The reinforcement was admirable. “Anatomy”—Aubrey reports—“was then little understood by the University and I recollect that Dr. Petty kept a body that he brought by water from Reading, a good while to read on, some way preserved or pickled.”

<sup>10</sup> Fitzmaurice, p. 3.

<sup>11</sup> Fitzmaurice, p. 14.



But the circumstance which established Petty's medical fame throughout the country-side, is associated neither with class-room nor clinic. The particulars, as detailed by Fitzmaurice, are curious enough to warrant citation in full:<sup>12</sup>

One Ann Green had been tried, convicted, and executed at Oxford on December 14, 1651, for the murder of her illegitimate child. Her execution seems to have been carried out with a combination of clumsiness and brutality characteristic of the times. It was observed "by the spectators that she seemed to take an unconscionable time in dying, so her friends went to assist her in getting out of this world, some of them thumping her on the breast, others hanging with all their weight upon her legs, sometimes lifting her up and then pulling her down again with a sudden jerk." At length the Sheriff was satisfied, and the unfortunate woman was certified to be dead. The body was then cut down, put into a coffin, and taken to the dissecting room. When, however, the coffin lid was opened she was seen to be still breathing and to "rattle," "which being observed by a lusty fellow who stood by, he, thinking to do an act of charity in ridding her out of the reliques of a painful life, stamped several times on her breast and stomach with all the force he could." Just at this moment, however, Dr. Petty and Dr. Wilkins appeared on the scene, and recognising distinct signs of life, decided to attempt to revive the supposed corpse. They wrenched open Ann Green's teeth, poured cordials down her throat, and persuaded a woman to go to bed with her to restore warmth. Signs of life soon began to appear; the doctors bled her, ordered her a julep, and so left her for the night. In two hours she began to talk. The dead had come to life. Though legally defunct, she is said to have survived to marry and become the mother of children, in spite of the Sheriff and to the confusion of the hangman.

Soon after this event, perhaps in consequence of it, Petty was made vice-principal of Brasenose and succeeded to the chair of anatomy. Further academic distinction followed—the professorship of music at Gresham College—a less bizarre association in the days when the quadrivium was still an academic tradition, than in our own times.

The residence in Oxford repeated in major scale the stimulating contacts of his Paris sojourn. A notable group interested in chemico-medical studies had gathered there in refuge from the stress of civil disorder, and we are told that: "In these stormy times they used, for the convenience of inspecting drugs, to meet at Dr. Petty's lodgings at an apothecary's house, as he was acknowledged to bear away the palm from all competitors in the experimental side of natural philosophy."<sup>13</sup>

In 1651 Petty obtained a two years' leave of absence, with the intention perhaps of further travel and study on the continent. But this plan was abruptly changed and the whole subsequent course of his life fashioned by his appointment as physician-general to the army in Ireland.

In this capacity Petty reorganized the medical service of the army, "reducing that affair," as he claimed, "to a state of easiness and plainness which before was held a mystery, and the vexation of such as laboured to administer it well." Opportunities for private study were not lacking. Robert Boyle described how, "in the course of experiments in anatomy,

<sup>12</sup> Fitzmaurice, pp. 18-19; based upon the contemporary account "News from the Dead" (Oxford, 1651), described by Hull in "Works," xv. The incident actually occurred in 1650.

<sup>13</sup> Fitzmaurice, p. 20.

which they at this time carried out together, he had satisfied himself of the circulation of the blood, and the freshly discovered *receptaculum chyli*, made by the influence of the *venae lactae*; and had seen especially in the dissection of fishes, more of the variety of the contrivances of Nature and the majesty and wisdom of her author, than all the books he ever read in his life could give him convincing notions of."<sup>14</sup>

But the activities of Petty as physician were drawing to an end, and his career as economist and economic administrator opening up. The determining circumstance was his selection by the government to conduct a survey of Ireland, preliminary to the allotment of forfeited lands among the troops, after the suppression of the insurrection. Petty received large tracts in payment for his services, and this, together with judicious purchases, laid the basis of the family fortune. Much of his energy was thereafter absorbed in defending his land titles and in managing his extensive property.

Returning to London, Petty associated with a group of followers of the new philosophy and was instrumental in founding the Royal Society in 1662, and became a charter member of its council. He was one of the charter fellows of the College of Physicians in Dublin and aided in founding the Dublin Philosophical Society, to whose proceedings he contributed various papers. He was knighted in 1662 upon the incorporation of the Royal Society and died in London in 1678. "If I were a prince, I should make him my second counsellor at least," was Evelyn's estimate, while Pepys added he was "the most rational man that ever I heard speak with a tongue."

Petty's economic writings represent the literary productivity of the last twenty-five years of his life. They are still obtainable in original editions, though rare; but they have been made accessible in an admirable reprint edited with scholarly apparatus by Professor Hull of Cornell University and published in 1899 by the Cambridge University Press.

These writings are all more or less directly associated with Petty's residence in Ireland and the resulting political intercourse. They were not "conscious elaborations of some economic system, more or less clearly conceived," but "each of them, on the contrary, was prompted by some circumstance of the times, and addresses itself, in fact if not in form, to some question of the day."<sup>15</sup> Thus the "Treatise of Taxes and Contributions"—the earliest and most systematic of Petty's economic writings—grew out of the changes in the revenue which the Restoration occasioned. The "Verbum Sapienti" is due to the costliness of the recoinage project of Halifax. The various essays in "Political Arithmetick" were probably animated by the purpose of establishing the great strength of London as against Paris. The studies of the "Dublin Bills of Mortality," the "Treatise of Ireland" and the "Political Anatomy of Ireland" represented the direct use of materials collected in or suggested by his interest in Ireland.

How much Petty the economist was influenced by Petty the physician appears in the title "The Political Anatomy of Ire-

<sup>14</sup> Fitzmaurice, p. 22.

<sup>15</sup> Hull, lxi.



land"<sup>16</sup>—a manner of natural history of the island, suggested by Chamberlayne's "*Angliae Notitia*"—and even more in the preface to the book:

Sir Francis Bacon, in his *Advancement of Learning*, hath made a judicious Parallel in many particulars, between the Body Natural, and Body Politick, and between the Arts of preserving both in Health and Strength: And it is as reasonable, that as Anatomy is the best foundation of one, so also of the other; and that to practice upon the Politick, without knowing the Symmetry, Fabrick, and Proportion of it, is as casual as the practice of Old-women and Empyricks.

Now, because Anatomy is not only necessary in Physicians, but laudable in every Philosophical person whatsoever; I therefore, who profess no Politicks, have, for my curiosity, at large attempted the first Essay of Political Anatomy.

Furthermore, as Students in Medicine, practice their inquiries upon cheap and common Animals, and such whose actions they are best acquainted with, and where there is the least confusion and perplexure of Parts; I have chosen Ireland as such a Political Animal, who is scarce Twenty years old; where the Intrigue of State is not very complicate, and with which I have been conversant from an Embrion; and in which, if I have done amiss, the fault may be easily mended by another.

'Tis true, that curious Dissections cannot be made without variety of proper Instruménts; whereas I have had only a commin Knife and a Clout, instead of the many more helps which such a Work requires: However, my rude approaches being enough to find whereabouts the Liver and Spleen, and Lungs lye, tho' not to discern the Lymphatick Vessels, the Plexus, Choroidus, the Volvuli of vessels within the Testicles; yet not knowing, that even what I have here readily done, was much considered, or indeed thought useful by others, I have ventur'd to begin a new Work, which, when Corrected and Enlarged by better Hands and Helps, I believe will tend to the Peace and Plenty of my Country; besides which, I have no other end.

It is to Petty's studies in "political arithmetic," however, that the historian of economic science ascribes the largest importance. There are interesting doctrinal contributions in the papers on currency and taxation; but the quasi-statistical studies possess a more general significance. Petty, as we have noted, was one of the group of experimental investigators, working in the spirit of the "*Novum Organum*" who began the systematic pursuit of scientific knowledge in England. When economic problems forced themselves upon his attention, it was inevitable that Petty should attempt their solution by the same scientific methods and with the same fundamental assumptions—the uniformity of law, quantitative precision, experimental test—that had figured in his earlier studies in medicine and in mechanics.

To economic study, pursued in this spirit, Petty gave the name "political arithmetic"—a beginning of what is now called statistics, but differing therefrom in that it undertook to reach conclusions upon matters as to which available data were much too inadequate to permit generalizations by bare statistical inference. Thus Graunt and not Petty is recognized as the founder of statistical science, because limiting his inquiry to the bills of mortality—the one field in which a considerable body of enumerated facts was at that time

available—Graunt laid the basis of such study both in method and result.

Petty's studies, on the other hand, in giving wider extension to this method—even involving extravagant, almost ludicrous, exploitation of insufficient data—first emphasized the need and stimulated the collection of economic facts. For almost a century, political arithmetic continued to be regarded as the device whereby economic principles could be formulated. After the labors of David Hume and Adam Smith had definitely established political economy as a form of social philosophy, political arithmetic lapsed definitely into an outgrown creed. Thereafter none too unworthy to cast a stone:

Hail! most prudent Politicians,  
Hail! correct Arithmeticians,

jeered the *Rolliad* in 1785. A few year later the "new-coined name" of statistics crept unobtrusively into England, and in 1801, with the definite returns of the first census, all possibility of political arithmetic serving as a technical economic method came to an end.

None of Petty's medical writings are accessible. None were ever published (with the bare exception of an abstract of a paper on mineral waters contributed to the Dublin Philosophical Society), and our only clue is a list of his works left by Petty himself and reprinted both by Fitzmaurice and by Hull. The medical entries are as follows:

- 1645 (Holland). *An History of Seven Months Practice in a Chemical Laboratory.*
- 1646 (Paris and Oxford). *A Discourse in Latin, "de Arthritide et Lue Venerea"; and "Cursus Anatomicus."*
- 1649 (Oxford). *Six Phisico-Medicall Lectures, read at Oxford.*
- 1650 (London). *Three Osteological Lectures.*
- 1651 (London). *Collection of Experiments.*
- 1652 (London). *Pharmacopœa and formula Medicamentorum.*
- 1652 (London). *Observationes Medicæ et Praxis.*
- 1653 (Ireland). *De Plantis. Notæ in Hippocratem.*

It is possible that certain of these are preserved among the Petty MSS. in the possession of the Lansdowne family at Bowood. Such is certainly the case with his inaugural lecture as professor of anatomy at Oxford on the growth and present position of medicine, from the MS. notes of which Lord Fitzmaurice quotes a tantalizing paragraph. As to the other items he gives no hint, while Professor Hull, whose opinion is peculiarly competent, writes me:

To my great regret I do not know anything of Petty's medical writings, indeed I never knew more of them than appears in the bibliography in Vol. II of his writings, which does not seem to indicate that any of them were printed. The Hester Anna Green pamphlet is probably not by him, and is scarcely medical in any event. To the best of my recollection I could find nothing detailed on his medical or anatomical performances.

It would be an extremely useful service if some student in this company, interested in the history of medicine, should undertake, perhaps in the course of a visit to England at some more propitious time, to determine this uncertainty, and even—if the event make it possible—to compile a *précis* or calendar of Petty's medical papers.

<sup>16</sup> [1672] London, 1691.



Far less chequered and eventful is the life of François Quesnay. Born at Méré near Versailles in 1694, the son of an advocate and landed proprietor of modest circumstances, Quesnay's childhood was spent in deliberate neglect of formal instruction, curiously anticipating Rousseau's doctrine that it is best to strengthen the body before wearying the mind. Up to his eleventh year he was unable even to read, while, on the other hand, the life of the fields and the habits of the countryside entered into his very being.

Once supplied with books, the mental pace was rapid. Natural science—botany, physics, chemistry, mathematics—and, above all, medicine attracted him. At sixteen he was apprenticed to a local surgeon, passing thence to Paris for more systematic study. In due course he qualified as a master surgeon and settled down to practice at Mantes. His life here was that of a hard-working country physician, gaining the confidence of his community, winning appointment in the hospital at Mantes, and adding to his store of experience.

His practice extended to the chateaus of the neighborhood and led to acquaintance with the Maréchal de Noailles. The acquaintance ripened into regard and friendship, opening up influential avenues of acquaintance, even to presentation to the Queen, by whom he was thereafter summoned whenever she visited Maintenon.

Quesnay first attracted notice by the publication in 1730 of a tract in criticism of a treatise on bleeding written by Silva, then head of the medical profession of Paris. At first ignored as a presumptuous impertinence, the validity of the critique "founded upon the laws of hydrostatics" was admitted, and the modest surgeon of Mantes entered the medical world of Paris.

With Noailles as sponsor, Quesnay was introduced to La Peyronnie, first physician-surgeon of the King. Peyronnie, in the hope of elevating the practice of surgery, then separated from medicine and often associated with the art of the hairdresser, had in 1731 obtained the establishment of the Academy of Surgery. He recognized in Quesnay a valuable acquisition and attached him to the new institution in the capacity of perpetual secretary, after having secured for him the appointment of surgeon-ordinary of the King. Quesnay was installed in the household of the Duke of Villeroi as physician and the way opened for distinction and reward.

Madame de Pompadour bestowed the grace of her patronage, and Quesnay became in turn first physician-ordinary and first physician-consultant of the King. The King himself found enough profit in Quesnay's company to call him familiarly "mon penseur," probably, as Mr. Higgs observes,<sup>17</sup> a play upon words—the French verb *panser*, to give medical and especially surgical assistance, lending itself to a pun upon *penser*, just as a blood-letting barber was styled "*le seigneur* (saigneur) *barbier*." In any event Louis mitigated the jest by conferring letters of nobility upon Quesnay and selecting in person his arms—three pansies—and the device "*propter cogitationem mentis*."

At a time when opportunity and intrigue rather than merit and virtue made men and determined careers, it is not surprising to find a more picturesque explanation of Quesnay's rise. Lord Crawford, the earliest editor of the memoirs of Madame du Hausset, lady-in-waiting of Pompadour, tells the story:<sup>18</sup> The Countess d'Estrades, then the favorite of Pompadour, while receiving a visit from the Duke of Villeroi was taken with sudden indisposition. Villeroi hurriedly called his physician, Quesnay, whom he had left waiting in his carriage. Recognizing that the Countess was subject to epilepsy and that she was on the verge of an attack, Quesnay with admirable discretion reassured Villeroi, ordered sedatives, dismissed the company with the explanation of "nerves," and then ministered to the unfortunate lady. The Countess—consciousness regained—realized her debt. She spoke to her mistress Pompadour of Quesnay's skill and discretion, with the result that Madame took him as her own physician, gave him apartments adjoining her own at Versailles and obtained for him the appointment of "*médecin ordinaire du roi*."

From the publication of the critique of Silva in 1730, Quesnay's scientific activity was marked. As secretary of the Academy of Surgery, he not only edited the memoirs of the society, contributing papers and prefaces thereto, but bore the brunt of the acrimonious controversy which the faculty of medicine waged for seven years against the new Academy of Surgery to determine the respective provinces of the two professions.

Unlike Petty, Quesnay published his medical writings and had the satisfaction of seeing them enjoy wide circulation and successive edition. The Surgeon-General's Library contains practically all of the texts—indeed some whose authorship is not beyond doubt—and intelligent summaries are found in Oncken's edition of the "economic and philosophical" works. There have also been various appreciations of Quesnay's work within the medical profession itself:<sup>19</sup> M. Bouisson read a memoir upon Quesnay under the title of "*Un Chirurgien-Economiste*" before the faculty of medicine of Montpellier in 1879. M. Ferrand contributed a paper on the medical work of Quesnay to the Paris Bulletin de l'Académie de Médecine in 1896. Cabanes has a gossip chapter on "*Le Médecin de Madame de Pompadour*" in his "*Cabinet Secret de l'Histoire*" (1897). A brief unsigned feuilleton on "*Franz Quesnay, Leibarzt Ludwig XV*," appeared in the *Deutsche Medicinische Wochenschrift* in 1901.

In order of publication the more important works are as follows:

- Observations sur les effets de la saignée . . . . (Paris, 1730).
- Histoire de l'origine et des progrès de la chirurgie en France (Paris, 1744).
- Traité de la gangrène (Paris, 1749).
- Traité de la suppuration (Paris, 1749).
- Traité des effets et de l'usage de la saignée . . . . (Paris, 1750).
- Traité des fièvres continues . . . . (Paris, 1753).

<sup>18</sup> Oncken, p. 115 n.

<sup>19</sup> Index Catalogues of the Library of the Surgeon-General's Office, sub "Quesnay."

<sup>17</sup> Higgs "Physiocrats," Appendix, Note A.



The "Treatise on Fevers," published in 1753, was the last of Quesnay's medical writings. Then in his sixtieth year, driven by weakened eyesight to forego surgical practice, this stoppage might well be accounted the inevitable advent of intellectual dulness. As a matter of fact, it marked the beginning of his larger service. Just as Petty the anatomist yielded to Petty the political arithmetician, so Quesnay the court-physician was succeeded by Quesnay the political economist. It is a curious coincidence that an exact hundred years separates the turning points. But with this the parallel ends. Petty was but thirty when the change came, with almost as many of his best years still before him; Quesnay had reached his sixtieth year with the inevitable end almost in sight. It is possible, too, to lay finger upon the precise events responsible for Petty's transition. In the case of Quesnay, this is far from clear and commentators diverge widely in their opinion. Garnier contends that Quesnay's study of the physiology of the human body tended to direct his attention to the physiology of the social body, and to the search for those uniformities which might be expected to prevail in social and economic relations. Higgs maintains that Quesnay's economic studies were inspired by Richard Cantillon's "Essay upon the Nature of Commerce," published in 1755, and that the school of the physiocrats dates from the interview in July, 1757, of Quesnay and Mirabeau. Oncken and Weulersse, making profounder analysis, call attention to the increasing restlessness of French philosophical writers of the early eighteenth century as to the economic abuses and financial ills of the kingdom, finding expression in the burst of independent thought which followed the Peace of Aix-la-Chapelle in 1748.

It is likely that the real explanation involves some part of each of these opinions. From early childhood Quesnay had seen the nourishing richness of Mother Earth, and the desperate poverty of those who cultivated her. Paris and Versailles rounded out the contrast—an industrious artisan class eking out a bare existence and a parasitic court drawing a golden fund from land ownership only to squander it in wanton excess. Obviously, it was distribution, not production, that wrought the poverty of the nation. Nature was bounteous, but the apportionment was at fault.

The initial task was to ascertain the principles governing the distribution or "circulation" of wealth. The conviction that there must be such uniformities or laws was an inevitable heritage from Quesnay's interest in natural science—a phase of that same enthusiastic endeavor to formulate principles of economic action which Montesquieu's "Spirit of Laws" represented in France, and David Hume's "Moral and Political Essays" embodied in England.

Quesnay's earliest economic writings were two articles on "Farmers" and "Cereals," contributed in 1755-6 to the *Encyclopédie* of Diderot and D'Alembert. The first presents an intelligent discussion of agricultural conditions in France, but contains little of theoretical importance. In the second article, "Cereals," we have a much more significant exposition of Quesnay's views. The essay sets forth that the true economic policy of France was not to stimulate manufactures, but to develop

the great productive powers of the soil. Agriculture is the real and the only source of national wealth. Farming is the true basis of prosperity and the rent of the landlord is the source from which public taxes should be paid. Free trade in commerce and laissez-faire in industry are essential to national well-being. The essay concludes with fourteen maxims of government, summarizing these arguments into a programme of practical reform.

In 1756 Mirabeau published his "L'Ami des Hommes." In essence, a commentary upon Cantillon's neglected essay, the work gave circulation and vogue to economic liberalism. The author became the popular idol, and the book ran through forty editions. In scholarly circles, too, there was response. Quesnay read the book and was stirred by it. A personal meeting followed, Quesnay expounded his own philosophy, with the result that Mirabeau became an ardent disciple and Quesnay agreed to attempt a precise formulation of doctrines.

The resulting performance was the "Tableau Oeconomique"—the *tour de force* upon which Quesnay's fame as an economist rests, and a work of some moment in the general history of literature. The circumstances surrounding its publication are in themselves of interest.<sup>20</sup> "The tactful Pompadour" persuaded Quesnay to forego his intention of public issue, and, in lieu thereof, to print it privately at Versailles in December, 1758. Only a few proofs were struck off, and it was long supposed that all of these were lost, the Tableau itself being available only as incorporated in later writings. In 1890, however, Dr. Stephen Bauer discovered among the manuscripts of Mirabeau in the Archives Nationales at Paris, a copy of the Tableau slightly revised by Quesnay himself, and this copy was reproduced in facsimile by the British Economic Association in honor of Quesnay's bicentenary in 1894.

The Tableau proper is a chart or graph covering a quarto page and designed to show visually the results of agricultural production. Starting out with the assumption of six hundred livres a year devoted to agriculture, the Tableau traces the circulation and partition of this among various economic classes to the end of locating the social surplus. In the matter of rapid intelligibility, the chart has been conservatively described as "a ludicrous failure." Francis Horner records that the Earl of Lauderdale, a distinguished economic writer of the pre-Ricardian period, never left the accursed zigzag without evaluating himself as a block-head, and to later students it stands alone—or, at most, associated with John Stuart Mill's "fourth fundamental proposition concerning capital"—as the *pons asinorum* of economic exposition.

What Quesnay meant that the Tableau should make clear, and what to the brilliant coterie that speedily gathered about him, it apparently established was: Agriculture alone is the source of national wealth. Whereas industry and commerce are sterile, at best yielding enough to replace the labor and capital involved therein, the cultivation of the soil yields a net product. Inasmuch as this *produit net* is the only true national revenue, so should it be the only object of taxation.

<sup>20</sup> Higgs, p. 42.



The state should be supported by a single, direct tax or *impôt unique* levied upon land. Finally, there should be no interference of any kind on the part of the state with the activities of individuals engaged in the production and circulation of wealth.

Quesnay's remaining economic writings took the form of contributions to the "Journal of Agriculture" and the "Ephemerides"—organs of the sect. He later reverted to mathematical studies, and in his old age he came to believe that he had solved the problem of squaring the circle. With the death of Louis XV, Quesnay lost court favor, and he died at Versailles on December 16, 1774.

Quesnay's doctrines were developed and popularized by a remarkable group of philosophers and savants, styling themselves "the economists," but better known in J. B. Say's phrase as "the physiocrats"—Mirabeau, Du Pont de Nemours, Mercière de la Rivière, Baudeau, Le Trosne, and Saint-Peravy. Gathered in disciple-like veneration about their sage, this gifted group constitute the unique example of an economic school or sect in the history of the science. By meetings, by journals and by writings, its members spread the doctrines of physiocracy over France and over Europe. In the world of affairs, the influence made for economic freedom, for simplification of taxation, for encouragement of productive effort. In the world of thought, the contributions were recognition of economic uniformities, enthusiasm for economic study, and emphasis upon laws of economic distribution. The specific doctrines were ultimately discarded. The practical proposals were rejected. But the larger service endured. It was in something more than fraternal regard, in almost a scholar's prescience that Adam Smith conceived the purpose of inscribing the "Wealth of Nations" to the "very ingenious and profound author," the "modest and simple" founder of the physiocratic school.

#### DISCUSSION.

DR. WELCH: Dr. Hollander has done us a great service in giving us this beautiful presentation of the subject. It is a very valuable contribution.

It is very interesting to consider physicians who became distinguished in other branches of knowledge. I have myself been more or less interested in this subject, considering, for instance, physicians who have been classic scholars, physicians who have been astronomers, etc. It is not difficult to find physicians who are eminent in the natural sciences. Dr. Kelly, for instance, has brought out the physicians who have been botanists. There have also been zoologists. This is all more or less familiar ground. It is much less common to find those eminent in physical sciences, but still the list is interesting and considerable. Those who have become eminent in the social sciences are relatively few. I rather think this is due to the fact that medicine had become pretty highly specialized by the time the social sciences were developed. The points Dr. Hollander brought out as to the relationship between medicine and the social sciences were extremely interesting. So also is his list of physicians. I think there is perhaps one name that might be added—that of Copernicus, with his essay on money. He was educated in medicine and actually practised it.

The two names selected for special consideration—Petty and Quesnay—are of course very different. Each was the child of his time and a very good example. Petty belongs to the group

of men at Oxford and later at London developing the so-called new philosophy, himself the very heart of that group and one of the founders of the Royal Society. But no less so Quesnay, the child of the so-called philosophical century, and the chief representative in medicine among the encyclopedists, as they were named.

The relation of Petty to Graunt is very interesting. Graunt is doubtless the founder of the science of vital statistics. His materials were the bills of mortality collected in the hands of the parish clerks. This was an ecclesiastical function and it remained in the hands of the parish clerks until 1836, when the Birth and Death Registration Act was passed. It is very interesting to consider the influence which the analysis of the bills of mortality—that is, the returns and registration of births, marriages and deaths—has had upon the development of preventive medicine. Petty and Graunt were most interested in its practical bearings. Edmund Halley, a contemporary of Sir Isaac Newton, collected the Breslau tables. Süssmilch is regarded as one of the modern founders of statistics, but the practical application of the knowledge thus derived was really made in England partly in the eighteenth and partly in the early part of the nineteenth century.

It is interesting to note that some of the English physicians took local analyses in the towns in which they lived, going around on their own initiative and taking a census. There was even a questionnaire of seven questions, and from that they drew conclusions as to the importance of isolating cases of infectious disease, etc. It was in 1836 that the famous Birth and Death Registration Act was passed and the Registrar General's office established, twelve years before the Public Health Act of 1848. It was from the data collected by the Registrar General during these earlier years that these practical measures in hygiene and preventive medicine were introduced in England. In this connection one name should never be forgotten, that of Dr. William Farr, who was connected for over forty years with the work of the Registrar's office, and who is in many ways the most important and interesting in the whole domain of vital statistics. His letters published in the reports of the Registrar General are of course classics.

Quesnay is really an interesting character in medicine as well as in economics. He was a much more highly educated surgeon than most of his day and was really the spokesman of the surgeons after the establishment of the Academy of Surgery. One of the most acrimonious controversies in the whole history of medicine, and the most discreditable in many ways, took place in regard to the establishment of the Academy of Surgery. The Academy of Medicine wanted to keep the surgeons back in every way, but finally they succeeded in getting the royal assent to the establishment of the Academy of Surgery. Quesnay was the second secretary. He it was who edited the Memoirs. His preface to the first volume is well worth reading. It is rather interesting to consider who was the champion on the other side. His is a name that started a line of thought and investigation and is as famous perhaps as Quesnay's. Astruc was the Professor of Medicine in the Faculty of Medicine when Quesnay was the secretary of the Academy of Surgery. Astruc is best known in medicine by his two great volumes on the venereal diseases, which still have much historical interest. It was Astruc who discovered the two sources or documents in the Pentateuch—the distinction between the Eloistic and Jeovistic writings. This work opened the path for all the later higher Biblical criticism. It is interesting that on the one hand we have Quesnay, the surgeon, as a contributor to economics, and on the other his great opponent, Astruc, identified with the first important work in the so-called higher criticism of the Bible—his famous conjectures on the sources which Moses had at his disposal for writing the Book of Genesis.

I have brought here the familiar translation by Otley of some of Quesnay's writings. His remarks on wounds of the brain are most interesting, with his plea for careful surgical intervention



in diseases of the brain, based upon an analysis of cases that came to post-mortem examination.

DR. GARRISON: Nothing, of course, could be added to the subject which Dr. Hollander has so admirably presented. We came over to be instructed and have learned a great deal. I have two books with me which may have some interest. One is the fourth impression of John Graunt's "Natural and Political Observations" (1665), which throws considerable light on the origin of vital statistics in England. Mr. Froude begins his History of England (Reformation period) with the observation that the growth of the population at that time was very slow, on account of the wars, epidemics, etc. All through the sixteenth century there was practically no increase. John Graunt says that "Bills of Mortality" were first made in 1592 and resumed in 1603, and that "the rise of keeping these Accompts was taken from the Plague." He gives a very curious account of the method of gathering vital statistics:

"10. We have hitherto described the several steps whereby the *Bills of Mortality* are come up to their present state; we come next to shew how they are made, and composed, which is in this manner, *viz.*: When any one dies, then, either by tolling, or ringing of a Bell, or by bespeaking of a Grave of the *Sexton*, the same is known to the *Searchers*, corresponding with the said *Sexton*.

"11. The *Searchers* hereupon (who are ancient Matrons, sworn to their Office) repair to the place, where the dead Corps lies, and by view of the same, and by other enquiries, they examine by what *Disease* or *Casualty* the Corps died. Hereupon they make their Report to the *Parish-Clerk*, and he, every *Tuesday*-night, carries in an Accompt of all the *Burials* and *Christnings*, happening that Week to the *Clerk* of the *Hall*. On *Wednesday* the general Accompt is made up, and Printed, and on *Thursday* published,

and dispersed to the several Families, who will pay four Shilling *per Annum* for them."

Graunt's book is very gossipy and entertaining as to the different medical statistics taken. His synopsis of contents and his observations show him to have been a man of untrained mind with a clever capacity for shrewd observation here and there, suggesting some one thinking aloud.

The other book is the second edition of "Die göttliche Ordnung in denen Veränderungen des menschlichen Geschlechts" of Süssmilch (1742), the most important work on vital statistics in the eighteenth century. It is said that the merits of Süssmilch are that he obtained better results than Petty and Graunt by using larger figures. Perhaps he came to that in this way: Early in the eighteenth century, there came to England one Abraham de Moivre, a mathematician and refugee from France, who was driven out by the revocation of the Edict of Nantes. At that time, gaming was very common in England and a gambling debt was accounted a debt of honor, to be paid before grocers', tailors' or other tradesmen's bills. A great interest was thus taken in the doctrine of chances, *e. g.*, the probability of any facet of a die turning up in a given number of throws. De Moivre is said to have made his living by solving problems of this kind for gamblers in a tavern in St. Martin's Lane. In 1716 he published his "Doctrine of Chances," which states most of the theorems between Pascal and La Place. In vital statistics, as in dice throwing, the probability of occurrence and recurrence is the more constant the greater the number of chances. With this knowledge, Süssmilch got better statistical results than his predecessors, and by applying Deparcieux's idea of "mean expectation of life" (1746), he made the first life table (1746), which was used in Germany all through the eighteenth century for actuarial calculations.

## COMMON ORGANISMS IN HEATED MILK: THEIR RELATION TO ITS REACTIONS.

By L. P. SHIPPEN, M. D.

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The organisms surviving in milk after heating at various temperatures have an especial interest on account of the importance attached to pasteurization. Flügge<sup>1</sup> in Germany, and Ford and Pryor<sup>2</sup> in this country have shown that the spore-bearing group is very resistant, and Ayers and Johnson<sup>3</sup> and other observers have found that in milk heated to and kept for a certain time at temperatures ranging from 60 to 75° C. there exist, in addition, many varieties of non-sporulating bacteria. In the following paper an attempt has been made to identify the most common of these organisms, to ascertain roughly the temperatures at which they are recovered, and to observe what relation they bear to the reactions of the milk in which they occur.

For this purpose, milk was obtained from the stores in the vicinity in sterile flasks and was transferred in the laboratory to sterile test tubes, especial care being taken not to allow any milk to come in contact with the cotton plugs. The tubes were then placed in a water-bath previously raised to the required temperature, and held at 60, 65, 70, 80 and 85° C. for 15 minutes, after which they were plunged into cold water for five minutes. By this method the milk was kept at the

desired temperature for from ten to thirteen minutes, as control tubes showed that it required from two to five minutes for the milk to assume the heat of the water-bath.

These tubes were incubated for two days and at the end of the first and second days the milk was plated upon plain agar and upon dextrose agar. The plates were studied after two days' incubation, and their colonies transferred to slant agar and to milk. Whenever necessary, plating was again resorted to, in order to purify the cultures. No attempt was made to isolate organisms whose growth was so slow that their colonies did not appear until after two days' incubation, for it was felt that such bacteria could have very little relation to the comparatively rapid reactions occurring in heated milk.

The 60° milk, after one day's incubation, sometimes showed little change, sometimes was coagulated and at other times peptonized. In from two to four days peptonization was often complete, but quite as frequently only coagulation with the production of whey and acidity occurred. The reactions were very inconstant, ranging from a normal clotting to complete peptonization; and test tubes taken from one sample of milk often showed as wide variations as the test tubes from different



specimens. No gas formation was ever observed, nor did transfers to dextrose broth produce any gas. In this the observations of the writer are not in accord with those of Ford and Pryor, who found that milk heated to 60° C. often showed a violent gas production. This divergence may be explained by a consideration of the different conditions under which the experiments were made. In the cases in which gas was observed the workers used flasks of milk, in which anaërobic conditions prevailed, so that the anaërobic gas producers were enabled to produce some effect upon the milk. In our experiments, in which no gas formation was observed, test-tubes were substituted for the flasks, and in these aërobic conditions alone existed.

Plates of plain agar made from the milk after one and two days' incubation showed a bacteriological finding as inconstant as the reactions, and seemingly bore little relation to the coagulation or peptonization of the milk. In some cases the peptonized milk was found to contain few spore-bearing varieties, whereas in coagulated milk after one day's incubation the spore-bearers sometimes seemed to be the predominant species.

Various strains of *Streptococcus lacticus* were isolated in every instance. This organism is more properly termed *Bact. g ntherii*, as has been noted in a previous article,<sup>4</sup> but the name *Streptococcus lacticus* having been generally adopted the writer in this paper prefers to use the latter appellation. Usually it possesses the power of firmly and quickly coagulating milk, but many strains merely produce a slight acidity even after a week or more in the thermostat. The majority of cultures isolated from the 60° milk belonged to this latter type, although occasionally a strain was picked up which retained the power of rapid coagulation. However, in the experience of the writer, some strains of *Str. lact.*, which have very little effect on milk when inoculated by means of the platinum wire, may firmly clot this medium when vastly greater numbers are transferred. Thus, a tube of sterile milk may become firmly coagulated 24 hours after being poured upon an agar slant culture of a strain of *Str. lact.*, which had merely a slight acid-forming power when transferred to milk in the usual fashion. The organism was recovered both from coagulated and peptonized specimens and frequently in both cases, after the milk had been incubated for two days, was found to have overgrown the other species so that the plates of greatest dilution contained only this bacterium. When dextrose agar was used for plating the colonies were even more numerous, but when transferred to plain agar many of these refused to grow. When transferred directly to milk some of these strains coagulated this medium in a typical manner; others, like the majority of those growing on plain agar, merely produced a slight acidity.

The organism next most frequently encountered in the milk heated to 60° C. closely resembled a species previously identified<sup>4</sup> as *Bact. troilii* (*Bact. lactis longi* b, Matzschita). This organism is a short, gram positive bacterium, without motility, whose cultural reactions are similar to those of *B. fecalis alkaligenes*. The strains isolated from unheated milk slowly produced in this medium a definite alkalinity without pep-

tonization. Those recovered from heated milk frequently seemed to cause no change whatsoever. Some, however, showed properties corresponding to those mentioned in the original description, whereas others after several days caused a slight reduction of litmus. At times the organism occurred in great numbers and, like *Str. lact.*, overgrew the spore-bearers after the milk had been incubated for two days.

*Micrococcus cremoides* and a few unidentified organisms were isolated occasionally. However, they did not appear with any regularity and could not be considered as common bacteria capable of playing a definite part in the reactions of heated milk. No bacteria belonging to the *B. coli.* or *Bact. a rogenes* groups were encountered, nor were any other gas producers ever recovered.

The reactions of milk heated to 65° C. resembled in many ways those observed in the 60° milk. After one day's incubation some tubes were peptonized, others coagulated, still others remained unchanged and, as in the case of the 60° milk, tubes from a single specimen often showed as wide variations as those from different samples. In from two to four days peptonization usually occurred, occasionally with the production of a little gas. At times only a normal clotting was observed. Transfers to dextrose broth in fermentation tubes occasionally caused some production of gas, yet no gas-producing a robic organisms could be recovered either from the milk or the dextrose broth. Plates made from the milk at the end of the first day's incubation sometimes contained only colonies of the spore-bearing types. At other times *Str. lact.* and *Bact. troilii* also were present. In milk incubated for two days these organisms frequently were found to have overgrown the other varieties, so that their colonies would persist to the exclusion of the spore-bearing type in the plates of greatest dilution. Like the cultures of *Str. lact.* and *Bact. troilii* isolated from 60° milk, these strains usually produced little effect when inoculated into sterile milk; and upon plain agar many failed to grow. No other organisms were ever encountered.

The milk heated to 70, 80 and 85° C. became peptonized in from one to four days. Normal clotting was never observed; instead there was usually a relatively small coagulum containing gas bubbles. When transferred to dextrose broth a definite amount of gas was commonly produced. From this broth and from the heated milk only the ordinary non-gas-producing a robic spore-bearers could be isolated by the usual process of plating.

As a control to these results, the thermal death-points in milk of the non-spore-bearing bacteria recovered were roughly estimated by the following method: Fresh cultures of the organisms were transferred to sterile milk, and heated in the water-bath to 60, 65 and 70° C. and kept for 15 minutes under conditions identical with those used in the previous experiments. *B. typhosus* was taken as a control. The results were found to be very irregular, when the cotton plugs and the surrounding glass of the milk tubes were not sterilized after inoculation. But when the mouths of the test tubes were thoroughly flamed and the corks burnt after inoculation but before the heat was applied, the results became constant.



Under these circumstances *B. typhosus* was killed at 60° C. The strains of *Str. lact.*, *Bact. troilii*, and *M. cremoides* isolated from milk heated to this temperature survived. At 65° C. *B. typhosus* and *M. cremoides* were killed, but *Str. lact.* and *Bact. troilii* survived. At 70° C. all these organisms were killed. It is worthy of note that all the strains of *Str. lact.* tested did not survive 65°. As mentioned in a previous paper, many strains recovered from unheated milk were found to have a thermal death-point below 60° C.

Of the bacteria isolated from the milk heated to 60 and 65° only the spore-bearers and the various strains of *Str. lact.* and *Bact. troilii* could be considered of frequent occurrence, and the cultural characteristics of these organisms do not completely explain the diverse reactions of the milk in which they are found. This milk either coagulated, usually with the expression of much whey, or else became peptonized after from one to four days' incubation, and in addition also showed gas production under certain conditions. Now *Str. lact.* will coagulate milk, but does so with the production of very little whey, and although the aërobic spore-bearers peptonize milk, they never act very rapidly and, in the writer's experience, do not cause any peptonization during the first few days in the presence of *Str. lacticus*. None of the aërobic organisms isolated produced any gas. Hence the rapid peptonization, marked whey formation, and evolution of gas observed in milk heated to 60 and 65° remain unexplained by what we know of the individual reactions of the organisms isolated.

From milk heated to from 70 to 85° C. only the common spore-bearers were recovered. Such milk peptonizes in from one to four days, usually with the production of a coagulum and the evolution of much gas. Yet the aërobic spore-bearers found therein form no gas in milk and peptonize it slowly, usually without coagulation.

The discrepancy between the reactions of the organisms isolated and the reactions of the milk in which they were found was most marked in the case of the specimens heated to from 70 to 85° C. Despite the fact that such milk commonly showed an evolution of gas after incubation, from it no gas producer could be isolated by aërobic methods. However, Ford<sup>1</sup> and Pryor<sup>2</sup> have recovered the anaërobe, *Bact. welchii*, from milk of this character and have shown that this gaseous reaction probably is due to its influence. They were unable to demonstrate the bacterium in milk heated to 60 and 65° C., but since it was found to exist in milk heated to from 70 to 85°, its presence in specimens heated at lower temperature may be assumed.

This bacterium, in addition to producing gas, has a strong acidifying, coagulating, and whey-producing power in milk when grown anaërobically and for this reason it was thought that the gaseous and other unexplained reactions observed in milk heated to from 60 to 65° might be due to its influence when acting in conjunction with the aërobes surviving the temperatures mentioned. In order to test this theory an attempt was made to reproduce the reactions noted in milk heated at temperatures ranging from 60 to 85° C. by the aid

of *Bact. welchii* and the aërobic organisms surviving these temperatures.

With this end in view two strains of *Bact. welchii* were isolated from two samples of 80° milk by a simple method, which is given here in detail, along with another method, as they afford an easy means of recovering *Bact. welchii* in pure culture.

The tops of the closed arms of ordinary fermentation tubes were removed, as in the type designed by Hill, and the resulting apertures tightly corked. One of these tubes was filled with 2 per cent dextrose broth and sterilized in the autoclave at a pressure of 20 pounds. Immediately after cooling it was inoculated with milk which, after being heated to 80° and incubated, showed the presence of gas. Then the fermentation tube was incubated for 24 hours, at the end of which period turbidity appeared throughout the broth and gas was observed in the closed arm. The opening of the bowl was tightly corked and the stopper in the arm carefully removed so as to prevent any mixing of the fluid in the bowl with that in the arm. Then a transfer was made from the arm to the bowl of a similar tube of freshly autoclaved dextrose broth. This preparation was incubated and, after the appearance of turbidity and gas, a similar transfer was made and the process repeated four or five times until the transfers made from the bowl to plain slant agar failed to show any growth when incubated under aërobic conditions. Hanging drops made from such cultures revealed only bacteria indistinguishable morphologically from *Bact. welchii*, and from such preparations it was impossible to isolate any aërobic organism.

When the dextrose broth was not freshly autoclaved, or when daily transfers were made from the bowls instead of from the arms of the fermentation tubes, this phenomenon did not occur. Instead the aërobic spore-bearers continued to grow along with *Bact. welchii* and occasionally even outgrew the latter organism so that no trace of it could be found.

However, it was observed that the fermentation tubes containing mixed cultures of *Bact. welchii* and aërobic and probably anaërobic spore-bearers usually became sterile in from two to five days, and this peculiar reaction led to a second even simpler method of isolating the organism in question. Welch<sup>3</sup> in his original paper has stated that in the tubes of Liborius *Bact. welchii* died in three days, when grown in pure culture and kept aërobically. It was found that in mixed cultures of spore-bearers in dextrose broth in fermentation tubes under these conditions the bacterium died in from three to five days, but that its death was preceded usually by that of the other spore-bearers with which it was mixed. Hence it was often possible to obtain a pure culture of *Bact. welchii* by making a simple transfer on the second, third and fourth days from the bowl containing the mixed culture to freshly autoclaved dextrose broth in fermentation tubes. Sometimes such transfers were sterile, sometimes they contained mixed cultures; in other cases only the aërobes survived. Usually, however, in one of these transfers it was impossible to demonstrate any organism but *Bact. welchii*.



Thus it appears that in freshly autoclaved dextrose broth in the closed arm of the fermentation tube *Bact. welchii* has the power of quickly outgrowing other aërobic and probably anaërobic spore-bearers, and that in the bowl it frequently kills the other spore-bearers before its own death.

As an additional precaution the two cultures obtained by the first method were first plated upon dextrose agar and then replated upon rabbit-blood agar. These two strains were found to correspond very closely with the organism as originally described. They were gram positive, rather large, encapsulated bacteria which caused the typical gaseous reaction in the dead rabbit, and had the power of producing gas in sugar-free agar and broth, as well as from dextrose, lactose and saccharose. They did not grow under aërobic conditions, but produced their reactions in the hydrogen jar, and in the fermentation tube when incubated under atmospheric conditions in freshly autoclaved media containing any one of the sugars considered. They varied somewhat from each other as regards the original description in the time required to produce their action upon milk, and in the amount of whey expressed. In this medium in the fermentation tube both produced an armful of gas and a coagulum riddled with gas bubbles, and caused the expression of so much whey that peptonization was suggested. One strain completed this reaction in 24 hours. The other in this time produced only an armful of gas without any coagulation. However, in 48 hours the two preparations became indistinguishable. Grown in the hydrogen jar in freshly autoclaved milk in test tubes the rapidly acting strain produced in 24 hours the same effect as in the fermentation tube under atmospheric conditions. The other, slowly acting, strain in this time coagulated the milk with the evolution of gas, but with the expression of very little whey.

These two cultures of *Bact. welchii* were now inoculated into milk in combination with each of the organisms previously found capable of surviving the various temperatures considered, in order to observe the influence of the growth of one of the bacteria upon the growth of any one of the remainder.

*Str. lacticus*, *Bact. troilii*, *B. mesentericus vulgatus*, *B. cereus* and *B. subtilis* were taken as representing the most common species existing in heated milk. Other non-sporulating organisms isolated from milk heated to 60° C. were not considered, since their presence therein is inconstant. The reactions of the two strains of *Bact. welchii* were found not to differ materially when inoculated into milk with the other bacteria employed. Likewise the reactions of the three aërobic spore-bearers, *B. mesentericus vulgatus*, *B. cereus* and *B. subtilis* resembled each other very closely, when grown in union with *Str. lacticus* or *Bact. welchii*. Hence it was possible, except in one instance, to simplify the experiment by eliminating the slowly acting strain of *Bact. welchii* and by taking *B. subtilis* as representing the aërobic spore-bearing group.

When *Bact. welchii* was transferred along with *Str. lacticus* the resulting reaction was identical with that seen when *Str. lact.* alone was inoculated into milk. But when transferred with either *Bact. troilii* or *B. subtilis* there occurred in from 24 to 48 hours a condition similar to that noticed in milk

inoculated with *Bact. welchii* when incubated under anaërobic conditions; the milk was coagulated and rendered violently acid; the coagulum was riddled with gas bubbles, and in addition peptonization or marked whey production was produced.

*Bact. troilii* grown with *B. subtilis* or *Str. lacticus* produced no visible change from the reactions caused by the latter organisms when transferred singly to milk.

When *B. subtilis* was inoculated into milk with *Str. lacticus* the reaction of the latter organism was hastened, that of the former inhibited. Thus in 24 hours the two bacteria produced in milk a soft coagulum, whereas alone *Str. lact.* did not cause this result until 2 days had elapsed. The peptonization produced by *B. subt.* in 48 hours when grown singly did not appear until the end of a week, and then was too slight to be absolutely definite.

Next the influence of heat upon the bacteria already mentioned was studied by comparing their reactions in milk with those which occurred when the milk was heated after inoculation.

The culture of *Str. lact.* selected possessed a thermal death point between 65 and 70° C. This strain caused acidity without coagulation after 24 hours. In 2 days it produced a solid coagulum with very little or no whey and reduced the litmus. In 3 days more whey was expressed, but no peptonization or gas production was ever caused.

When after inoculation the milk was heated to 60 and 65° for 15 minutes, the time of the reaction was lengthened slightly in the former case, markedly in the latter. Thus, in the milk heated to 60° C. there was produced in 48 hours a soft, instead of the hard, coagulum noted in the unheated specimen. But after heating to 65° only acidity occurred in the same length of time, and coagulation was delayed until 4 days had elapsed, at which period the condition was practically identical with the reaction occurring in 2 days in the unheated control.

The strain of the *Bact. troilii* used had little or no effect upon litmus milk in 48 hours. Later it produced a slight reduction of the litmus. No other reaction was ever noticed. Its thermal death point was found to be between 65 and 70° C., but its action upon the milk was produced too slowly to be affected by the heat applied.

*B. subtilis* caused no change in milk in 24 hours. After 48 hours it produced a slight peptonization, which became marked in 3 or 4 days. There was no definite coagulation. The reaction was faintly acid. After heating to 60° beginning peptonization was delayed until 3 days had elapsed, and did not become marked until after 4 days.

*Bact. welchii* failed to grow in milk in test-tubes under aërobic conditions.

An attempt was now made to reproduce the reactions occurring in milk heated to temperatures ranging from 60 to 85° by means of the organisms surviving therein. Milk heated to 60° either coagulates with the expression of varying amounts of whey but without gas production, or else becomes peptonized. Under certain conditions gas is formed. In it *Str. lact.*, *Bact. troilii*, *B. subt.* and *Bact. welchii* survive. When these organisms were transferred to sterile milk and incubated, the



medium became riddled with gas and reacted very much like that inoculated with *Bact. welchii* alone, when grown anaërobically. This experiment would seem to indicate that *Str. lact.* without the application of heat, is not capable of hindering the reaction of *Bact. welchii*, which occurs in the presence of the spore-bearers and *Bact. troilii*, and this in spite of the fact already noted that *Str. lacticus*, unaided by heat, inhibits the effect produced by the aërobic spore-bearers upon milk. Thus it would seem that the coagulation with little or no gas or peptonization observed in raw milk requires the influence of some other organism. In this connection it is worthy of note that when *Bact. aërogenes*, a common inhabitant of unheated milk, was added to the mixture, the milk coagulated in a manner similar to that usually seen in unheated market milk.

When, after inoculation with the four organisms first employed, the milk was heated to 60°, a different result was obtained. Under these conditions the growth of *B. subtilis* is delayed while the action of *Str. lact.* is inhibited very slightly. In consequence the latter organism dominated the reaction and produced in 48 hours a result similar to that seen in 60° milk when it curdles without gas or peptonization.

A second result was obtained when the entire contents of an agar slant culture of *B. subtilis* was transferred to a test-tube of milk and the usual amounts of *Str. lact.*, *Bact. troilii* and *Bact. welchii* were added and the heat was applied. Here *B. subtilis* dominated the reaction and peptonized the medium in 24 hours. In addition a small gaseous coagulum showed that *Bact. welchii* had been enabled to act. In this case the result again was similar to one at times observed in 60° milk, and evidently was due to the overwhelming amount of *B. subtilis* used in the experiment. It suggests that the peptonization at times observed in 60° milk may be due to the presence therein of an excessive amount of aërobic spore-bearers.

Milk heated to 65° reacts in a manner similar to that of 60° milk, but under this condition peptonization with gas production is more common. From it may be isolated the same four organisms. When these bacteria were transferred to sterile milk and the medium was heated to 65°, it became coagulated, peptonized and gaseous in 48 hours, thus reproducing the reaction noted. It is evident that here the heat used so delayed the action of *Str. lact.*, that it was unable to inhibit *B. subtilis*. The latter was thus enabled to grow and in this way cause *Bact. welchii* to develop and produce gas as it does when *B. subtilis* and *Bact. welchii* alone are transferred to milk. In this case a different result was obtained when *B. mesentericus vulgatus* and the slowly acting strain of *Bact. welchii* were substituted for *B. subtilis* and the rapidly acting strain of the latter organism. This combination produced in 24 hours only a slight acidity. In 48 hours it caused coagulation with the expression of much whey, but without evident peptonization and with the evolution of very little gas. This reaction is not unlike that which sometimes occurs in 65° milk.

Milk heated to from 70 to 85° in the writer's experience

contains only the aërobic and anaërobic spore-bearers. When *Bact. welchii* and *B. subtilis* were transferred to this medium and it was heated to 80°, coagulation with peptonization and gas production ensued after from 24 to 48 hours' incubation. This is the common condition observed in milk heated at the temperature considered. Thus it is seen to be possible by means of *Bact. welchii*, grown in union with the aërobes existing in heated milk, to simulate many of the reactions of the milk in which they are found.

#### CONCLUSIONS.

1. In milk heated to 60 and 65° C. for 15 minutes *Streptococcus lacticus*, *Bact. troilii* and the spore-bearers survive. They can be recovered from peptonized as well as from normally clotted milk, but their cultural activities do not completely explain the reactions of the milk in which they are found.

2. Other non-spore-bearing organisms are encountered occasionally in milk heated to 60° C. Their scarcity makes it seem probable that they play an unimportant rôle in the reactions of heated milk. They were not encountered in milk heated to 65° C.

3. No gas-producing aërobes were isolated from milk heated to 60° C.

4. From milk heated to 70 and 85° C. only the aërobic spore-bearers were recovered by the common method of plating. The cultural activities of this group do not explain the reactions seen in milk heated to these temperatures.

5. *Bact. welchii* assumes the power of growth in milk under aërobic conditions when transferred to this medium with the common aërobic spore-bearers or with *Bact. troilii* (Matzschita). Under these circumstances its reactions overwhelm those of the bacteria with which it grows.

6. When the organisms employed are heated to 60° C. *Streptococcus lacticus* inhibits the action produced upon milk by *Bact. welchii* in the presence of *Bact. troilii* and the aërobic spore-bearers, provided these are not markedly in excess.

7. *Streptococcus lacticus* fails to inhibit this reaction when the aërobic spore-bearers are present in vast numbers, or when no heat is applied.

8. It does so after heating to 65° only in the presence of a slowly acting strain of *Bact. welchii*.

9. The reactions observed in milk heated at temperatures ranging from 60 to 85° C. may be simulated, in the presence of *Bact. welchii*, by the growth of the aërobes commonly surviving the temperatures considered, after the application of the desired degree of heat.

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# THE RELATIONS OF SPLANCHNOPTOSIS TO GASTRIC ACIDITY.

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Opinions as to the relationship, if any, that obtains between the acidity of the gastric juice and the various grades of ptosis of the gastro-intestinal viscera, differ very widely. Lockwood, Aaron and Joseph Sailer claim that in ptotic stomachs hyperacidity is found more frequently than subacidity. Steele, Francine and T. R. Brown hold that diminution of free hydrochloric acid is the rule. Still a third group of investigators, including Boas, dismiss the matter with the statement that in cases of ptosis the results of chemical examination are variable, and for reasons not always readily discernible all kinds of deviation from the normal occur.

Lockwood, in a series of 250 cases, found that over four-fifths of the patients showed a normal or hyperacid gastric juice. He gives the following table, but does not state just how the results were computed.

	Per cent.
Achylia was present in.....	9.5
Subacidity was present in.....	8.0
Normal acidity was present in.....	55.6
Hyperacidity was present in.....	27.4

In a series of gastric analyses as large as the above there will always be found a considerable number of cases that cannot be classified simply as belonging to one of the three groups of normal acidity, hyperacidity, or diminished acidity cases, for the very good reason that many of them fall in more than one group. A patient may belong to the normal acidity class as regards his free hydrochloric acid, and at the same time show hyperacidity for his total acids; and, conversely, his total acidity may fall well within the normal limits (40-60), while his free hydrochloric acid is much below the accepted normal (20-40).

In the writer's series of 200 examinations, 42 such overlapping cases were found. There were 19 cases in which the free hydrochloric acid was normal, with the total acidity well over 60. One patient, with a free hydrochloric of 27, showed a total acidity of 92. A second, with a free hydrochloric of 32, had a total acidity also of 92. These two patients may truly be said to have had a hyperacidity, but not a hyperchlorhydria. In 18 cases the total acidity was found to be normal, with the free hydrochloric either below or above normal. One patient, with a total acidity of 50, showed a free hydrochloric of 5; another, with a total acidity of 48, had a free hydrochloric of 0. Five patients showed a normal free hydrochloric acid co-existent with a total acidity below the normal.

How are such cases that fall in two different groups to be classified? Obviously the only possible way that insures mathematically accurate results is to consider all cases from the view-point (a) of increased or diminished acidity as regards the free hydrochloric acid alone; and (b) of increased or diminished acidity as regards the total acids alone. No other procedure is reasonable, and any analysis not taking

this fact into consideration is meaningless. This point, which we consider of much importance, may possibly help to explain the conflicting reports and widely diverging views of many writers regarding the relations of splanchnoptosis and gastric acidity.

Among his conclusions Lockwood says: "The acidity in gastroptosis depends largely upon the degree of the associated atony; the more marked the atony the greater is the tendency toward hyperacidity." Francine, from a study of 70 cases, reports: "There was a slight diminution in free hydrochloric acid with no or slight dilatation, while as the dilatation became more marked the free hydrochloric acid diminished, and was absent in most of the patients in very high grades of dilatation; thus suggesting that the subsequent dilatation is of more importance than the ptosis as regards the gastric secretions." Thus both authorities, while reaching opposite conclusions, agree that in ptotic stomachs the acidity depends largely upon the amount of associated atony.

The present study was undertaken to accurately determine the effect that ptosis of the stomach and bowel have upon the gastric juice, without any consideration of the causal factors underlying this effect. How these secretory changes have been brought about, whether by circulatory interference due to pressure and position, by reflex irritation through drag and pull on the sympathetic plexus, or whether they are the result of atrophy and atony, has not been entered into. Our purpose is to report the findings in a series of 200 thoroughly worked up and verified cases of splanchnoptosis. The cases all occurred in patients who applied for relief, from many and various digestive symptoms, to the gastro-intestinal clinic of The Johns Hopkins Hospital Dispensary, and who in the course of routine examinations were discovered to present well-marked instances of ptosis. The diagnosis was in every case confirmed by fluoroscopic examination, the method being to administer one ounce of bismuth subcarbonate 18 hours previously, and a like amount immediately before the fluoroscopic examination.

The cases have been arbitrarily divided into three groups according to the degree of descensus, and designated as instances of ptosis of the first, second or third degree, respectively. In first-degree cases are included patients in whom the greater curvature of the stomach reached to the level of the pelvic brim; in second-degree cases those in whom the greater curvature was found below the level of the pelvic brim; and in third-degree cases those in whom the stomach reached to the bottom of the pelvis.

The gastric analyses were made after the usual Ewald test-breakfast of one slice of bread and 250 cc. of water; the stomach contents being aspirated 45 minutes after ingestion. The test-breakfast was, as a rule, fairly well digested and showed no constant abnormality. In expressing normal, increased, or



diminished acidities, the usual text-book figures of 20-40 for the free hydrochloric acid and 40-60 for the total acid have, of course, been used.

There were 110 females and 90 males. The high proportion of males is extremely interesting, inasmuch as many authorities still regard splanchnoptosis as an ailment largely peculiar to women, and, according to the statistics of one recent writer, females are more frequent sufferers than males in the proportion of 7 to 1.

The ages varied from 15 to 76 years; over 60 per cent of the patients being between 20 and 40 years of age. No patient under 15 years of age is treated in the clinic.

There are 25 cases of ptosis of the first degree, 140 cases of the second degree, and 35 cases of the third degree. As one would expect, the most frequent accompaniments of the ptosis were adhesions and atony. Marked adhesions were present in 40 cases and marked atony in 50 cases.

It is of interest to note that the average amount of stomach contents recovered by aspiration after the test meal increases with the degree of descent of this organ.

In ptosis of the first degree the average amount recovered was ..... 41 cc.  
In ptosis of the second degree the average amount recovered was ..... 56 cc.  
In ptosis of the third degree the average amount recovered was ..... 72 cc.

*First Degree Ptosis.*—In this group, comprising mild cases in which the greater curvature reached no lower than the level of the pelvic brim, were found 25 cases—14 in females and 11 in males. The gastric analysis gave the following results:

FREE HYDROCHLORIC ACID.	
	Per cent.
Normal acidity was present in.....	40
Hyperacidity was present in.....	28
Subacidity was present in.....	20
Achylia was present in.....	12
Subacidity or achylia was present in.....	32

TOTAL ACIDITY.	
	Per cent.
Normal acidity was present in.....	32
Hyperacidity was present in.....	48
Subacidity was present in.....	20

*Second Degree Ptosis.*—In this group of moderate ptosis, comprising those cases in which the greater curvature reached below the level of the pelvic brim, were found 140 cases—73 in females and 67 in males.

FREE HYDROCHLORIC ACID.	
	Per cent.
Normal acidity was present in.....	49.2
Hyperacidity was present in.....	12.8
Subacidity was present in.....	24.2
Achylia was present in.....	13.5
Subacidity or achylia was present in.....	37.7

TOTAL ACIDITY.	
	Per cent.
Normal acidity was present in.....	46.4
Hyperacidity was present in.....	18.5
Subacidity was present in.....	35.1

*Third Degree Ptosis.*—This group, including those high-grade ptoses in which the stomach was found at the bottom of the pelvis, contained 35 patients—23 females and 12 males.

FREE HYDROCHLORIC ACID.	
	Per cent.
Normal acidity was present in.....	48.5
Hyperacidity was present in.....	25.7
Subacidity was present in.....	17.1
Achylia was present in.....	8.5
Subacidity or achylia was present in.....	25.6

TOTAL ACIDITY.	
	Per cent.
Normal acidity was present in.....	40
Hyperacidity was present in.....	34.2
Subacidity was present in.....	25.7

From these tables it would appear that no definite relationship can be established between the degree of ptosis and that of diminished acidity, the cases of the second group showing a much lower acidity percentage than those of either the first or third. An average of these three tables gives the following percentages for the 200 cases of ptosis of all three grades.

FREE HYDROCHLORIC ACID.	
	Per cent.
Normal acidity was present in.....	48
Hyperacidity was present in.....	17
Subacidity was present in.....	22.5
Achylia was present in.....	12.5
Subacidity or achylia was present in.....	35

TOTAL ACIDITY.	
	Per cent.
Normal acidity was present in.....	43.5
Hyperacidity was present in.....	25
Subacidity was present in.....	31.5

#### CONCLUSION.

1. The free hydrochloric acid was found to be normal or diminished in 83 per cent of all cases. The total acidity was normal or diminished in 75 per cent of all cases. Therefore, it would seem quite conclusive from these figures that in *ptotic stomachs there is a general tendency toward diminished acidity; and that hypochlorhydria and achylia are more frequently met with than hyperchlorhydria, the ratio being about 2 to 1.*

2. It is of interest to note that the 50 cases complicated by marked atony gave a still higher percentage of diminished acidity than the cases in which atony was not so marked, as is shown in the following table:

#### FIFTY CASES OF SPLANCHNOPTOSIS OF ALL DEGREES WITH MARKED ATONY.

FREE HYDROCHLORIC ACID.	
	Per cent.
Normal acidity was present in.....	42
Hyperacidity was present in.....	18
Subacidity or achylia was present in.....	40

TOTAL ACIDITY.	
	Per cent.
Normal acidity was present in.....	36
Hyperacidity was present in.....	30
Subacidity was present in.....	34



Apparently the acidity in gastroparesis is largely influenced by the amount of associated atony—the greater the atony, the lower the acidity.

3. *Achylia* was present in 12.5 per cent of all cases. This at first sight seems to be a rather high figure. Lockwood, however, reports that in his experience achylia was present in nearly 7 per cent of all patients applying for relief from

gastro-intestinal disorders. The difference between these figures is hardly great enough to suggest a causal relationship between the two conditions.

To Dr. Thomas R. Brown, at whose suggestion this report is made, I wish to express my most sincere thanks for the privilege of studying these cases.

## PROCEEDINGS OF SOCIETIES.

### THE JOHNS HOPKINS HOSPITAL MEDICAL SOCIETY.

APRIL 19, 1915.

#### 1. The Blood and the Blood Vessels in Hemophilia and other Hemorrhagic Diseases. (Abstract.) DR. ALFRED T. HESS, New York City.

It is impossible at the present time to classify the hemorrhagic diseases. However, two main groups may be distinguished: hemophilia and purpura. By hemophilia is meant the type of disease which is characterized by its hereditary nature and by the fact that it is transmitted almost always to the male, the female showing no manifestations of the disease. Clinically, its main criterion is the great delay in the coagulation of the blood. The purpuras, on the other hand, show an almost normal coagulation time of the blood, and occur in females as frequently as in males. This group is characterized by a diminished number of the blood platelets, which are normal in hemophilia; by an increase in the bleeding time; by the occurrence of hemorrhage at the site of subcutaneous puncture; by the appearance of many small petechial spots, and by the freedom of the joints from hemorrhagic involvement. In addition to these signs, we have described what may be termed *the capillary resistance test*, which is chiefly present in the purpuric conditions and has been found to be absent in hemophilia. By this is meant the phenomenon of the appearance of petechial spots on the fore arm following the application of a tourniquet for a definite period to the upper arm, in other words, after subsection of the vessel walls to this increase of pressure.

However, these two groups of hemophilia and purpura overlap to a certain extent. We have met with an instance where true hemophilia existed in the male, and purpura, manifesting the various symptoms just enumerated, was present in the female. Furthermore, purpura not infrequently occurs as a family disease, so that a hereditary history does not indicate the existence of hemophilia. There are other borderline cases.

Melena neonatorum is one of the most important groups under purpura. From a pathogenetic point of view, this must not be considered an entity. It includes the toxic, hemophilic and purpuric type.

The defect leading to hemophilia is not definitely known. It has been generally determined that there is no deficiency of calcium. In one case followed for a considerable period, a definite deficiency of calcium was established. This was determined by means of the calcium estimations of the blood, by the hastening of coagulation following the addition of minimal amounts of calcium to the blood (a procedure which delays or does not hasten the coagulation of normal blood), and by metabolism studies which show that in this case there was a negative balance of calcium, whereas in a typical case of hemophilia, the calcium balance was positive. This case, a boy of about 4 years, was judged to have hemophilia, as the coagulation of his blood was delayed and the platelet count was always normal.

The blood vessels vary in their resistance greatly among normal children. They were found to be somewhat weak among children having tuberculosis. In a study of numerous cases of infantile

scurvy, we were led to conclude that the blood was but slightly influenced by this disorder, but that the hemorrhages, so characteristic of this disease, were due to involvement of the blood vessels.

From a clinical standpoint it would seem that too much stress is at present being laid upon the coagulation time of the blood and even from blood obtained not directly from the blood vessels. Operations are undertaken if the clotting time is reported as normal. This leads to serious or fatal consequences. It is far more important from this point of view to ascertain the number of platelets, the bleeding time, and the appearance or absence of hemorrhage following subcutaneous puncture.

#### 2. Experimental Removal of the Pineal Body. DR. W. E. DANDY.

A satisfactory method of approach to the pineal, with removal, was demonstrated, with drawings by Mr. Broedel of the different steps in the operation. The operation as evolved has been the result of three years of unsuccessful attempts, the animals invariably dying from intraventricular hemorrhage. This was due to the necessity of opening the ventricles and a bleeding which occurred synchronously.

The first attempts to remove the pineal, and which were finally successful, were by an approach under the corpus callosum and under the great vein of Galen, following the interquadrigeminal group to the pineal. It was finally decided that the difficulties of approach, the time which it consumed and the capricious results necessitated a new method. This new method is very simple and can be done in from one-half to one hour on very young puppies. In this method the corpus callosum is split posteriorly for a short distance and the roof of the third ventricle perforated, releasing the fluid, when the pineal is beautifully exposed under the great vein of Galen at its origin upon the two small veins of Galen. By this method about 30 animals between the ages of 10 days and one year were pinealectomized, and all with perfectly negative result. There was absolutely no evidence of any precocity, either sexual, somatic or mental. This is the first successful operative procedure for the removal of the pineal body.

APRIL 26, 1915.

### THE ETIOLOGY OF TYPHUS EXANTHEMATICUS.

(Abstracts.)\*

#### 1. Bacteriological Studies. DR. HARRY PLOTZ, New York City.

In a preliminary communication published in the *Journal of the American Medical Association*, of May 16, 1914, I described an organism which I considered to be the etiological agent in typhus exanthematicus. Since that time I have had the opportunity of studying a much larger series of cases, and the results together with the serological and experimental studies have confirmed the opinion then expressed. The differentiation of the mild endemic form of typhus fever seen in New York from other

\* Complete reports will be published shortly in the *Journal of Infectious Diseases*.



fevers is due to the clinical insight of Dr. Nathan E. Brill. The similarity of typhus fever had been noted clinically, and the striking cross immunity experiments of Anderson and Goldberger demonstrated that the condition was most likely a mild form of typhus fever. As our studies give the definite proof that these cases are instances of typhus fever, we shall designate the European cases, epidemic typhus fever, and the New York cases, endemic typhus fever.

It had been demonstrated by early experiments that the virus exists in the circulating blood during the febrile period of the disease and that the virus is not filtrable. Ricketts and Wilder pointed out that the disease need not necessarily be caused by a protozoon, although it be insect-borne. Aerobic cultures made by different observers and by myself proved negative.

Up to the present time we have studied 11 cases of European epidemic typhus fever and 40 cases of the local endemic form of the disease. The former were studied through the kindness of Dr. Joseph J. O'Connell, health officer of the port of New York, and the latter through the courtesy of the attending physicians of Mount Sinai Hospital. The work was carried out under the direction and with the helpful assistance of Dr. E. Libman. We are indebted to Dr. F. S. Mandlebaum, pathologist of the hospital, for many courtesies and for the facilities of the laboratory.

Aerobic studies, made according to the method of Rabinowitch, all proved negative. Anaerobic studies were carried out according to the method introduced by Veillon, modified in that serum glucose agar originally suggested as an optimum medium by Libman, was used instead of glucose agar. All ascitic fluids used were thoroughly studied aerobically and anaerobically, the presence of hemoglobinophilic organisms being excluded by their use.

Colonies of the organism usually appear in from three to 16 days. After they have developed they are inoculated on slants of  $\frac{1}{2}$  per cent serum glucose agar, the tubes then being inserted into Buchner tubes. The colonies usually appear in the lower two or three centimeters of the tube. There is first a small opaque spot which grows larger and is surrounded by a brownish area of precipitation. On cross-section the colony is Y-shaped, brownish in appearance and soft in consistency. The arms of the Y are fusiform.

The organism is a small pleomorphic Gram-positive bacillus, which is non-motile, non-encapsulated and not acid fast. Most of the organisms are straight, occasional ones are rounded or slightly pointed; coccoid forms also occur. Degeneration and involution forms appear early. Spores are not present. Polar bodies are occasionally demonstrable.

Besides the studies made in Buchner tubes, inoculations were made into a variety of media in the long tubes of the type used by Noguchi. There is no growth on agar or sugar-free bouillon after 20 days observation. Growth is present in  $\frac{1}{2}$  per cent glucose agar with ascitic fluid and kidney tissue, but is better in 2 per cent glucose agar. There is a minute flocculent growth at the bottom of the glucose bouillon tube after eight days.

In Buchner tubes, after three days on glucose serum agar, there is a creamy white growth which later may become light brown in color. There is moderate precipitation which increases on subculture. The growth on other media is described in the full publication.

The organism from the epidemic and endemic cases was found to produce acid and precipitation in glucose, maltose, galactose and inulin and not in raffinose, mannite, arabinose, saccharose, dextrine and lactose. The organism is an obligatory anaerobe.

The organism was recovered from the blood in seven cases of epidemic typhus fever during the febrile stage; it was recovered from an eighth case by culture of the blood from an infected guinea-pig.

Of 34 endemic cases, 53 per cent yielded the bacillus. In two endemic cases the organism was found in one, 12 hours, and in the other, 36 hours after the crisis. 198 control cases did not yield the organism. The organism occurs more frequently early in the

the disease. It occurs in larger numbers in the epidemic cases than in the endemic cases.

Considered in conjunction with the serological and experimental evidence which follows, these facts prove that this bacillus is the etiological factor in typhus exanthematicus. Following a very kind suggestion of Professor William H. Welch, the organism has been named *bacillus typhi exanthematici*.

## 2. Serological Studies. DR. PETER K. OLITSKY, New York City.

With the use of an antigen made up of strains of the typhus bacillus from endemic and epidemic cases, 11 cases of epidemic and 34 cases of endemic typhus fever were studied. Of 25 cases studied at the height of the disease, only two were positive. Of 10 cases studied at the crisis, four were positive. In the post-critical stage of the disease, nine epidemic and 30 endemic cases were investigated, and 71.8 per cent were found to give positive reactions. The maximum concentration was found to occur between the second and twelfth day after the crisis. Observations were made as regards duration of the antibodies. 104 control cases showed complete absence of complement binding bodies. Complement fixation studies made with the serum of typhus fever cases and antigens made from various organisms other than the typhus bacillus gave negative results.

Positive agglutinations were obtained in more instances than positive complement fixation tests. Only reactions in dilutions of 1-50 or higher were considered positive. Of 24 cases tested before the crisis, all were negative, except two which were tested one day before the crisis, both of which had a titre of 1 to 100. Of 10 cases tested on the day of crisis, three were positive and seven were negative. After the crisis, 38 cases were studied, 92.6 per cent of which were positive. Agglutinins have been demonstrated as late as five months after the crisis. Of a very large series of control cases no case had a reaction in a dilution of over 1 to 50 except three cases in which the occurrence of a previous attack of typhus fever could not be excluded. In these cases the reactions varied from 1 to 100 to 1 to 200. Control studies made by testing the serum of typhus cases against various organisms other than the typhus bacillus proved negative.

Investigations made concerning precipitation reactions showed that the curve was the same as that with the other antibodies, the most frequent results being obtained after the crisis. Serum from cases other than typhus fever gave negative results.

The opsonic index increases at the crisis and remains high in the convalescent stage of the disease. Similar rises were noted in artificially immunized serum (rabbit's). Phagocytosis is probably an important factor in overcoming the infection.

Cross-fixation investigations and cross-agglutination tests demonstrated that the organism obtained from epidemic typhus fever and the one from endemic typhus fever are two strains of the same bacterium.

A study of the serum of monkeys that had reacted to the typhus virus, showed that complement fixation and agglutination tests were usually positive after the crisis. The serum of immune guinea-pigs contained neither agglutinin nor complement fixing bodies. It is most probable that this animal develops its high grade of immunity by means of its tissue elements and only to a very slight degree by means of the circulating blood. Rabbits are not susceptible to the typhus bacillus in small amounts. When small yet increasing amounts of bacteria are given, they develop very potent immune serum.

The observations which I have described allow of only one conclusion—typhus fever is a reaction against the organism which has been isolated by Dr. Plotz.

## 3. Experimental Studies. DRS. GEORGE BAEHR, HARRY PLOTZ and PETER K. OLITSKY, New York City.

For the purpose of ascertaining whether the organism recovered from the blood of typhus fever patients was also found in animals having experimental typhus fever, a series of 24 guinea-pigs was



inoculated with defibrinated blood obtained from patients or animals with the disease. Blood for cultures was obtained by direct aspiration of the heart. From one-third of these guinea-pigs the same bacillus was isolated that had been obtained from the blood of individuals with typhus fever. The number of colonies found averaged about one per cubic centimeter of blood. The organisms were found most frequently in animals having severe reactions. The majority of the blood cultures were positive when taken between 24 and 72 hours after the onset of the fever. This is the time at which the fever is highest.

By inoculation of two strains of bacilli obtained from epidemic typhus cases, a typical reaction was produced in two guinea-pigs. The blood of one of these guinea-pigs was cultured on the third day of the reaction and the organism recovered. Other guinea-pigs or monkeys were later inoculated with these two strains of bacilli or with strains from other epidemic cases which had been in artificial media for more than three or four weeks, and all strains were found to have completely lost their virulence. In each instance the inoculation was followed only by a slight transitory rise in temperature during the first 36 hours, a reaction also observed in the experiments with virulent organisms and apparently due to a toxin reaction. After cultivation on artificial media for more than a month all strains of epidemic organisms lost this toxin action. The bacilli from endemic cases were found to lose their virulence outside the body still more rapidly than those from epidemic cases. These organisms were not only avirulent, but did not even possess the power of producing a toxic rise in temperature after inoculation, a property only lost by the epidemic typhus organisms after cultivation for over a month. The variation in virulence and in toxin production of the epidemic and endemic strains is the only essential difference which we have been able to demonstrate.

It was found that typhus blood which contains no bacilli or only very few bacilli is not infective for animals. It appears from a series of 57 experiments that infectivity is absolutely dependent upon the presence of a sufficient number of these bacilli. This in itself is conclusive evidence of their etiological significance.

Recently a study has been begun upon individuals who have merely been exposed to the infection of typhus fever. The interesting observation has been made that after the exposure some of these typhus contacts may react with the production of specific immune bodies without having had any clinical evidences of the disease.

#### DISCUSSION.

DR. ANDERSON: Mr. President: I consider it a very great privilege to have been present to-night and heard the three papers that have just been presented. As perhaps some of you may know, the question of typhus fever has been one in which I have been considerably interested for the past three or four years and I have had the privilege of contributing something to our later knowledge of typhus fever.

In this work but slight attention was given to attempts to cultivate the organism and our cultural methods were confined almost entirely to the use of the ordinary aerobic and anaerobic methods in order to demonstrate that the blood used in our experiments was free from extraneous organisms.

There is nothing that I can add to what the others have said, other than to say that the evidence presented here this evening appears to me to be almost convincing and I shall be surprised if the work here presented will not be confirmed very speedily by others.

I was especially interested in the statements as to the amount of blood necessary to be used in order to obtain a growth and note that the minimum amount of blood in which growth was usually obtained corresponds closely with the amount that we have employed to be surely infective for guinea-pigs.

With your permission, Mr. President, I should like to say just a few words in regard to the prevention of typhus fever.

I do not know of any experimental evidence to the effect that typhus fever is transmitted in any other way than by the bite of the body louse and possibly by the bite of the head louse. The fact that the disease may be caused by a bacterium does not necessarily preclude the possibility of transmission by other biting insects, but our experiments, as well as those of others, with fleas and bedbugs have all been negative. If, then, the louse is the chief means, or the only means, by which the disease is transmitted we are able, from this fact, to deduce certain fundamental factors in regard to the prevention of typhus fever and these may be broadly grouped under three headings:

First, the reduction of lice infestation among the population in general. This is, to a large extent, a question of education, except in institutions such as bath houses, lodging houses, and similar places where numbers of persons may congregate and over which the sanitary authorities may exercise control.

Second, the destruction of lice on the persons, and in the surroundings, of those suffering from typhus fever, of typhus fever suspects and contacts. This is a simpler procedure than the first one because, according to our experiments, the louse requires frequent feedings of blood in order to maintain life and therefore our attention under this procedure may be mainly directed to the destruction of lice on the patient and in the surroundings recently occupied by persons suffering from the disease.

The third measure is to prevent or minimize the chances of persons in contact with cases of typhus fever being bitten by lice. This applies especially to physicians and nurses in attendance upon cases of the disease.

An important practical point to bear in mind is that the "striking distance" of the louse, and therefore of typhus fever, is very much less than that of the flea, which transmits bubonic plague, and of the mosquito, which transmits malaria and yellow fever. Therefore, we may confine our attention, for practical purposes, to surroundings recently occupied by persons suffering from typhus.

I should like to suggest a fourth measure, which I believe would be advisable for those proposing to visit localities in which typhus fever is prevailing in epidemic form attended with high mortality. This measure is the inoculation with the so-called Brill's disease or mild typhus fever in order that an attack of the mild form of the disease may be induced in the individual, recovery from which would afford immunity against the virulent type. The case mortality in the United States from the mild form of typhus fever is certainly not over one in a hundred and perhaps less, while the case mortality in Serbia may be 20 per cent or possibly more.

I thank you very much.

DR. LIBMAN: I should like to say a few words for Dr. Brill who was anxious to come down here to-night, but was prevented from doing so by other engagements. He believes that the work that has been presented here to-night gives the definite proof that the cases which he described are cases of typhus fever. He was inclined to believe this when Drs. Anderson and Goldberger published their studies, but would not accept their work as final proof because he thought there might be a relationship between the two diseases such as exists between paratyphoid and typhoid fever. One other point is that while he believes it may very well be that typhus fever is transmitted only by the louse, there are several points that need elucidation as, for instance, the fact that the cases which he has seen in New York occurred quite as frequently in the warm as in the cold part of the year. Apart from this, the New York cases are almost never seen attacking a family.

It has been most interesting for us to watch this work. It was a very good example of what can be accomplished by a simple line of reasoning. Dr. Plotz saw a few cases of Brill's disease,



while he was a student, and thought he would like to find out the cause. Because the cases described by Dr. Brill were suspected of being instances of mild typhus fever he decided to use the methods which should be employed in trying to discover the etiological agent in typhus fever. He concluded to look for an anaerobic bacterium and found the organism in the first case which he cultured.

It is also interesting for us to realize the importance of previous investigations in this connection and to consider how many results have been obtained by American investigators.

Dr. Anderson has spoken of the possibility of having people who are to be exposed to European typhus fever inoculated with the virus from the Brill's type of cases and go through the disease. However, while it is true that the mortality in the endemic cases is trifling, patients suffering from the disease are often painfully sick. It might be wise if vaccines made from the organisms which are now on hand are not effective, to try the use of vaccines made from virulent organisms obtained from epidemic cases. Dr. Baehr's studies on contacts suggest that there might be a field for the use of vaccination with small numbers of living bacilli.

DR. WELCH: I was extremely interested a year ago when Dr. Plotz was kind enough to show me the results which he had obtained. Even then they were very promising. I do feel that these young investigators are to be most heartily congratulated. Their work is a model of thorough-going scientific accuracy. It is hard to see any point which they have not covered in the space of time at their disposal and with material necessarily limited in amount.

Dr. Libman spoke of the number of American investigators who have contributed. There is one name I should like to mention, whose memory should always be held in great gratitude, and that is young Dr. Ricketts, who died in Mexico as the result of typhus from exposure while working there. He had at the time just accepted the chair of pathology at the University of Pennsylvania. He was one of the most charming and brilliant investigators in the profession.

There are one or two points I would like to comment on. It is most interesting that this appears to be a true bacterium. I would like to inquire whether these investigators consider that there is anywhere a local or more than one local focus of the disease, and that the bacteria which are present in such relatively small numbers are swept into the blood perhaps, and that possibly this is the kind of bacterium which is well known to be associated with various other localized infections. That could hardly be worked out except on the basis of adequate post-mortem examinations. I do not know exactly where one would expect that local focus to be. Conceivably perhaps in the bone marrow. Some years ago we had a few cases of typhus fever brought here from Sparrows Point, and I remember that in examining the bone marrow in those cases, I was struck with some rather remarkable lesions. Is this anything more than a bacteriæmia, or is there a local infection somewhere? If a real bacteriæmia, it is perhaps the only true bacterial bacteriæmia in human pathology. I do not know of another example.

I was thinking all along of the points Dr. Baehr discussed at the end—of how to reconcile these results of the transmissibility of the disease by lice, when such a large amount of blood was needed to convey the disease. Dr. Baehr has probably said all that can be said at present on that point. He has also intimated that it may be that the louse seems to be the sole transmitter of the disease by virtue of the fact that it is a particularly favorable host for the multiplication of the organisms.

I was not quite clear as to one point, but I have no doubt I overlooked it, namely: After the animal has been infected with the culture of the organism—I quite understand that it is difficult and that the organism loses rapidly in virulence, so the number of

successful infections must be very few—and after an animal has passed through an infection due to the bacterial invasion, is it then immune from inoculation with the typhus blood? That would strengthen immensely the evidence and would be very significant.

DR. FORD: I think it is interesting to point out that in this disease some of the most important investigations have been carried out by American physicians. Thus, in 1839, Gerhard of Philadelphia first clearly pointed out the distinguishing features of typhoid and typhus, while the earlier papers of Jackson of Boston are also equally important.

I have here a copy of Gregory's book on fevers which I thought might be interesting to show because of the excellent descriptions given. It is interesting to note that Gregory himself expresses an opinion which we have heard expressed here this evening, namely: That of all fevers typhus fever is the most apt to be mistaken for other diseases.

In considering the historical development of our knowledge of typhus fever, how striking it is that so much of our modern knowledge of this disease has come from American investigators.

There are possibly five important points:

First, the differentiation of this disease from typhoid fever.

Second, definite determination that the disease can be transmitted to animals.

Third, mode of transmission through the louse.

Fourth, that we have in this country, both in Mexico and the United States, an endemic disease identical with the typhus fever of the Old World.

Finally, that the disease is bacterial in origin and that a positive agent can be obtained from the blood and identified.

With the exception of the work of Nicolle and his collaborators these advances in our knowledge of typhus fever are all due to the investigations of American scientists, a matter for which we have reason to feel justly proud.

DR. JANEWAY: There are one or two things I want to say to those of you who are occupying most of the benches here to-night. The first one is that this is a beautiful demonstration of the fact that no age is exempt from the possibility of great discoveries. Pasteur did his best work after a hemiplegic attack when along in middle life. Other investigators, as those who have come here to-night, have done remarkable things at the inception of their medical careers. This ought to be a constant stimulus to those of you who are about to enter on your hospital work—to know that a man in the first year of his internship in a hospital, has been able to put the finishing touches to the problem of the etiology of typhus fever, which has occupied many investigators for nearly a century.

Secondly, Dr. Libman is quite right in his statement that it is not his work. Nevertheless the work could not have been possible except in an environment in which the scientific pabulum for the production of ideas and the refining of methods were not already at hand. For that environment Dr. Libman is responsible. For years he has been founding in New York City what one might call a school of bacteriological study, particularly in blood culture work. There has been no place in the United States where more careful blood culture studies have been made than in the Mt. Sinai Hospital.

In the third place, it is rather wise for us to remember here that the intellectual and scientific atmosphere necessary for this kind of work is not found only in a university. Here is a beautiful piece of work from a hospital with no definite university association. I think that emphasizes perhaps what has been one of the vital points of the Johns Hopkins Medical School all these years—that a medical school without a hospital is even more apt to be sterile than a hospital without a medical school.

DR. BAEHR: Dr. Welch has asked as to the possible existence of some local focus from which the bacteria may be distributed



into the blood. We have searched for such a local focus in animals which have been killed during the course of the disease and have failed to find it in any of the viscera. It will prove interesting to follow Dr. Welch's suggestion and examine the bone marrow with this in view. In reply to Dr. Welch's second question, we can only cite the statements made in our paper that after a reaction produced with the bacilli we have not as yet had an animal live long enough to test its immunity.

The point brought out by Dr. Brill is also very interesting—that the families of individuals with endemic typhus fever very rarely develop the disease. This fact has been considered by some as militating against the identity of Brill's disease and epidemic

typhus fever. As many as four cases in one family have been reported in the literature, but this is very unusual.

The explanation may lie in the development of an immunity in the exposed members of a family, similar to that of Dr. B. and Miss L. The family of an endemic patient is exposed to the bites of the lice before their full infectivity has developed. Like Dr. B. and Miss L., they may therefore merely react with the production of antibodies without having had any febrile manifestations of the disease. Later, after the lice have reached the stage of full infectivity, these more or less immune relatives as well as the convalescent patient may act as carriers for their distribution to others.

## NOTES ON NEW BOOKS.

*Osler's Modern Medicine.* Second edition. Vol. III. Diseases of the Digestive System; Diseases of the Urinary System. (Philadelphia: Lea & Febiger, 1914.)

Following the policy adopted in the preceding volumes of the second edition we note the general condensation of the chapters by the elimination to a large extent of historical matter and citations from the literature. The work has been well done and the various chapters have been improved and brought up to date, although the absence of the literature deprives it to some degree of its air of authority. The letter press, paper and illustrations are much better than in the first edition.

Among the chapters in the digestive tract, the most notable are: Diseases of the Liver, Gall-bladder and Ducts, by A. O. J. Kelly, revised by Wm. Pepper; The Pancreas, by Opie; The Peritoneum, by Rolleston. In the urological section: Nephritis is covered by J. B. Herrick; Infections of the Kidney, by T. R. Brown; Lithiasis, Tumors, the Prostate, and Genito-urinary diagnosis, by H. H. Young. Altogether the volume is a distinct improvement on the first edition and, with the exceptions noted above, covers the subjects exceedingly well.

*Selected Addresses Relating to Education, Biography, Travel, etc.* By JAMES TYSON, M. D., LL. D., Professor of Medicine Emeritus, University of Pennsylvania. Cloth, \$1.75 net. (Philadelphia: P. Blakiston's Son & Co., 1914.)

The reader, at the outset, is most pleasantly impressed by the author's graceful and altogether unusual confession of his three-fold reasons for publishing these addresses. Would that all authors were as frank!

The addresses are all characterized by a directness, ease and felicity of expression which gives an added charm. They cover a wide range of educational, biographical and professional topics and, although not of equal merit, are all interesting. They display a deeper religious and spiritual tone than is generally to be found in the deliverances of physicians, who as a rule are little inclined to dwell upon the duty of joyousness, hopefulness, sympathy, faith or charity, or to recommend them to their auditors. The papers on "Hospital Organization," "The Trained Nurse," and the several phases of medical education are full of wisdom derived from large experience interpreted by an open mind.

The memoirs of Smith, Pepper and Gerhard show the heart of the writer and his keen insight into the personal characteristics of his intimate friends and professional associates. They are also worthy tributes to three men who contributed materially to the growth and development of medical science in Philadelphia.

The descriptions of Karlsbad, Vichy and the Engadine furnish a valuable analysis of the merits and demerits of these health resorts, as well as charming descriptions of the scenery and surroundings. His "repeated message," as he happily terms it, will be appreciated by all who read it.

*Osler's Modern Medicine.* Second edition. Vol. IV. Diseases of the Circulatory System; Diseases of the Blood; Diseases of the Lymphatic System; Diseases of the Ductless Glands; Vaso-motor and Trophic Disorders. (Philadelphia: Lea & Febiger, 1915.)

This volume is, in the reviewer's opinion, the best of the system so far issued. In diseases of the circulatory system the principal chapters are contributed by Hoover, Lewis, Babcock, Osler and Alexander Gibson. The section on congenital diseases of the heart, by Maude Abbott, is excellent. Nothing could be finer than Osler's discussion of aneurysm and those who remember his ward classes can renew their enthusiasm in reading this chapter. It would be hard to get together a better group of writers to cover all phases of cardio-vascular pathology.

Section II, on The Blood, is covered by Cabot, and The Hemorrhagic Diatheses, by Pratt, both parts being considerably changed and brought up to date.

In Section III, The Lymphatic System is by Warthin whose extensive pathological experience is very much in evidence; Longcope gives a fine presentation of Hodgkin's Disease.

Section IV, The Ductless Glands, is largely covered by Dock, who gives a good presentation of the modern theories without laying too much stress on any one. The last section, on Vaso-motor and Trophic Disorders, is entirely by Osler and in his best vein.

Were it possible for any system to hold this level of achievement throughout, the publisher and the reader would be mutually fortunate.

*Acute General Miliary Tuberculosis.* By G. CORNET, M. D., Berlin. Translated by F. S. TINKER, B. A., M. B., B. C., etc. Cloth, \$1.50. (New York: Paul B. Hoeber, 1914.)

The present volume gives an erudite review of the older literature upon this subject. The pathology and clinical manifestations of the disease are satisfactorily considered and the mechanical features, whereby the circulation is flooded with tubercle bacilli, are rehearsed in detail. The fact, however, that none of the important experimental work upon immunity in tuberculosis, which surely has an important bearing upon the subject, is so much as mentioned, gives the book a somewhat antiquated flavor and it seems a pity that the author has not brought it up abreast with the latest scientific thought. The translation is poor. L. H.

*Manual of Bacteriology.* By R. TANNER HEWLETT, M. D., F. R. C. P., D. P. H. Fifth edition. Cloth, \$4.50. (St. Louis: C. V. Mosby & Co., 1915.)

In this volume of 700 pages the author attempts to present and combine the subject matter in such a way that it may be not merely interesting from the standpoint of general bacteriology, but of special value in relation to clinical medicine and to hygiene or public health. In this respect it may be said to serve various



purposes. As a text-book, although somewhat elementary, it is thorough, complete and especially suited to beginners in bacteriology. Also to busy practitioners who desire to keep in close touch with this rapidly progressing science, it will serve a similar purpose. It is also useful as a reference book in that it summarizes the findings of others and gives the original literature. The conclusions reached in regard to some of the still undecided questions in bacteriology are worthy of careful study, because of the ripe experience of the author. The book may also serve as a laboratory manual in general or clinical bacteriology and in hygiene and sanitary investigations. The methods advocated for the bacteriological examination of water, air, soil, sewage, milk and foods are those made use of by standard public health laboratories.

In a brief survey of its contents we find a great deal of merit. The technique described for certain phases of bacteriological work is slightly different from that generally employed but of decided excellence. The descriptions of the methods employed in clinical laboratory diagnosis are brief, but afford all that is essential for beginners. Brief references are made to serum diagnosis, to vaccines and to the methods of their preparation. By including several chapters on higher schizomycetes, the pathogenic protozoa and on diseases, the causative agents of which are generally considered as filtrable viruses, the author adds completeness to his work. To the hygienist the entire volume is significant from the view-point of general bacteriology, but the chapters dealing with the bacteriology of water, air, soil, sewage, milk, foods and disinfection are of special importance.

W. W. F.

*The Commoner Diseases, their Causes and Effects.* By DR. LEONHARD JORES. Authorized translation by WILLIAM A. WOGLOM, M. D. Cloth, \$4.00. (Philadelphia: J. B. Lippincott Company, 1915.)

This is an excellent book, worthy of the widest popularity. The method of presentation will appeal to students and more particularly to internists, since it gives a pathological picture of disease that corresponds with the clinical picture observed during life. Instead of following the usual custom of describing the various lesions which may affect each organ, the author selects a disease and describes the changes commonly found in a body that has suffered from it. Thus widely scattered lesions are brought together under each caption, and their relation to one another is pointed out. The pathological descriptions are agreeably brief and yet give satisfactory impressions of the lesions. The discussions throughout are cogent and present the important recent developments of medical science. The author gives a broad, clear and interesting view of the relation of clinical medicine to pathology. The translation has been well done. The book has exceptional merit.

L. H.

*The Heart in Early Life.* By G. A. SUTHERLAND, M. D., F. R. C. S. Cloth, \$2.00. (London: Oxford Medical Publications, 1914.)

This publication is a readable little book of two hundred pages. It is nicely arranged and well printed. The subject matter is divided into three sections: Functional Cardiac Disturbances; Borderland Between Functional and Organic Disease; Organic Heart Disease. The various chapters in these sections deal with the physiology, diagnosis and treatment of the several conditions.

The author makes no effort towards the development of a text-book, but deals rather broadly with the clinical findings, normal and pathological, of the heart in childhood. He points out that the pathological physiology of the child's heart is definitely different from that of the adult and that, therefore, the symptoms and signs are distinctive. He emphasizes normal peculiarities of the youthful heart—the relatively large size, the instability of the vasomotor tone with the possible functional dilatation of the vessels or of the heart itself.

The book is well worth while, in that it points out a fact that is generally not fully comprehended—that in early life functional conditions far outnumber the organic diseases in cases of suspected "heart trouble," and that many of the symptoms, which are truly cardiac in adult life, in childhood are referable to other organs, especially to the nervous system. A diagnosis to be of avail cannot depend on the anamnesis or on the presence of an apical murmur. There must be a complete physical examination with a balancing of all the findings with the functional activity of the heart. And then, it will be found that many of the children who have been condemned to the abnormal life of the cardiac with all its pitiful demands should, like those unfortunate cases of postural albuminuria, be allowed the lives of normal individuals.

No inference can be made that the author does not agree with the complete protective treatment of organic lesions, but it is his purpose to emphasize the necessity of a full knowledge of the normal—the appreciation of the normal presence of a pulmonary systolic murmur, of an evanescent apical systolic murmur, of sinus arrhythmia and so forth.

There is very little new in the book, but criticism might be extended towards the absence of discussion of certain important cardiac phenomena. There are very few tracings, and their lack is almost always felt when one is dealing with cardiac study. But the author evidently only purposes to pick out interesting features of the cardiac functioning and to expand on them.

E. W. B.

*Medical Electricity, Roentgen Rays and Radium.* By SINCLAIR TOUSEY, M. D. \$7.50. (Philadelphia and London: W. B. Saunders Company, 1915.)

In this volume of 1200 pages the author has endeavored to cover the field of electrotherapeutics, roentgenology and radium. The portion on electrotherapeutics has been treated pretty thoroughly, and is up to date in literature and therapeutics.

The latter two subjects are still in the developmental stage; and, although the author has taken them up as thoroughly as possible, nevertheless, since the book has gone to press, a great many important discoveries have been made in both these lines. Then, too, on these two subjects the literature has not been kept up to date. The majority of the citations are from monographs published largely between 1906 and 1910, and in only two or three instances are references made to publications as late as 1912. This is especially true in the X-ray diagnosis of gastrointestinal diseases.

It is unfortunate that the author should have given such a short space to a subject so important that within the last three years it has engaged almost exclusively the attention of the roentgenologists, and in one instance only were we able to find any reference in this particular line of work later than 1912. The subject matter, however, has been handled well, and the salient points are illustrated by numerous cuts.

The mechanics and technique of the X-ray laboratory have been unusually well stated, and in a short space a clear conception is given of that part of roentgenology. The writer has made no attempt to go into details of differential diagnosis. He has simply given a brief description of the lesions and then has relied largely upon his photographic reproductions to illustrate the cases. He has done valuable work in summarizing the results of the various operators as to their findings in various conditions, such as in renal and ureteral calculi, and other kindred subjects.

As a reference work for the literature upon the various subjects, the book is very good indeed, except for the fact that it is not up to date.

F. H. B.

*A Handbook of Fevers.* By J. CAMPBELL McCCLURE, M. D. Cloth, \$3.50. (New York: Paul B. Hoeber, 1914.)

This compilation on the fevers is written distinctly from the point of view of a decade or two ago, and while pretending "to be no more than a handbook for the use of students and practitioners"



would seem to contain little that would appeal nowadays to the former, and perhaps even to the latter. The clinical descriptions, although poorly balanced, are graphic, and the introduction on the general management of fevers is sound and to the point; but in the sections on therapy the author's practice outweighs at times generally recognized methods of procedure, and in the section on etiology and epidemiology we are constantly surprised by speculation upon questions which for some time have been reduced to facts. Thus it is a shock to hear that "in the dirt and dust of houses, in unclean streets and back courts" the perishable meningococcus "may flourish and spread the disease"; or that diphtheria may arise in connection with some unsanitary spot like an unclean pigsty. Nor do we find any mention of the "carrier" so fundamental in the spread of the latter disease. In the section on therapy we find, in the face of modern views on liberal feeding in typhoid, that a piece of dry bread may be given in uncomplicated cases after the temperature has been normal for seven days. The practitioner is also advised to use opium in typhoid hemorrhage without any warning as to the masking of the early signs of perforation. The discussion of serum-sickness is quite inadequate, since it gives no idea of the actual possible dangers of primary and secondary serum injections. Again, in the employment of immunological terms the author is guilty of a looseness which is certainly unscientific. Thus, for instance, he speaks of plague and meningitis "antitoxins" and of "hyper-sensitized" instead of sensitized. The bracketing the names of Kolle and Wassermann, with those of Burroughs, Wellcome & Co., as makers of anti-meningitis serum would seem hardly in good taste, and finally, one's sense of the fitness of things is surprised by a section on such a very questionable procedure as the treatment of tuberculosis with contratoxin No. 4, a mixture of coagulant and hemolytic snake-serum and sheep's blood. The inclusion of malaria and kala-azar under the caption of fevers of known bacteriology might be criticised by a purist.

On the whole the book is pleasantly written and quite readable.

A. L. B.

*Medical Diagnosis.* By ARTHUR LATHAM, M. A., M. D., F. R. C. P., and JAMES TORRENS, M. B., B. S., M. R. C. P. (New York: The Macmillan Company, 1915.)

The authors were of the opinion that there exists a true need for a book in which there is arranged, in a concise and accessible form, all of the clinical information and the more important laboratory details which are necessary for the purpose of making a scientific diagnosis in medical conditions. To supply such a need the present volume of some 600 pages has been prepared, which covers the specific infectious diseases, tropical diseases, diseases of the blood, ductless glands, metabolism, cardio-vascular system, respiratory tract, gastro-intestinal system and the central nervous system. The final section of the book is devoted to certain diseases of the skin.

The method of handling each disease has been worked out along the lines of combining brevity with an excellent oversight of the essential clinical and laboratory findings which make for good diagnoses. It is obvious that not much space can be devoted to any one condition and necessarily some accuracy has been sacrificed to meet the demands of this book. For this reason the reviewer is of the opinion that students would do well to avoid the use of such a volume until after a thorough mastery of the subject had been obtained from larger and more exhaustive textbooks. A number of errors could be pointed out; thus, no mention is made of the phenolphthalein test for kidney function and the urea test given on page 412 has long since been consigned to oblivion by reason of its great inaccuracy. The short section devoted to the examination of the cerebrospinal fluid is practically of no value. The pictures, for the most part, are good, and the 19 colored plates are quite well done. It is certainly un-

fortunate that none of the ova of the more important worms are pictured.

On the whole the book probably represents as good a compend of medical diagnosis as is at present to be found.

*The Salvarsan Treatment of Syphilis in Private Practice.* By GEORGE STOPFORD-TAYLOR, M. D., M. R. C. S., and ROBERT WILLIAM MACKENNA, M. A., M. D. and B. Ch. Cloth, \$1.50. (New York: The Rebman Company, 1914.)

This little brochure is written in a pleasant chatty style quite different from the usual treatises. As the authors remark in the preface, the book records rather impressions and conclusions from their own work than a summary of the general status of the subject; hence one inclines less to criticise the frequent trite sayings and truisms scattered through its pages. The exposition of the microscopic methods of spirochetal demonstration is concise and to the point, but the same can hardly be said of the section on serum diagnosis. One is much surprised to find the author still advocating an inaccurate and misleading system which employs the native anti-sheep amboceptor and the complement of the patient's serum. An excellent sketch is presented of the technique to be observed in the preparation and injection of salvarsan and is followed by comments on its general action in the various stages of the disease, illustrated by interesting case reports. The dangers of salvarsan are treated altogether too lightly, but this standpoint is founded on the hitherto fortunate experience of the writers. On the whole, the book, while readable, is not to be recommended to one seeking information, unless he has previously familiarized himself with the subject.

A. L. B.

*Public Health Laboratory Work.* By HENRY R. KENWOOD, M. B., F. R. S., Edin. Cloth, \$4.00. (New York: Paul B. Hoeber, 1914.)

The present volume, of over 400 pages, is divided into six parts, each of which deals with a special subject.

What the author apparently intends to present in this volume is a chemical consideration of the questions arising in relation to public health, since only a brief mention is made of other phases of this type of work. For this reason it fails to meet the full demands of the day. What is needed above all is a compact laboratory manual, which does not narrow its sphere merely to the chemical side of the subject, but in its scope considers, briefly but accurately and comprehensively, the essentials of laboratory diagnosis. In the attainment of this object the science of bacteriology possibly stands first in importance, and yet in this edition hardly any reference to it is to be found.

The subject matter is well presented and the methods outlined, which in many instances do not correspond with the ones adopted by the American Public Health Association, are of considerable merit. They are evidently the summation of years of experience along practical lines. Analytical methods generally are difficult to describe in such a manner as to be both accurate and comprehensive, but in this volume we find them clearly outlined, their relative significance being given in detail without impairment of their comprehensibility.

A brief *résumé* of the subject matter may afford a general conception of the nature and character of the contents. The introductory chapter is of special merit and although somewhat elementary presents the essentials that form the foundation for thorough work along chemical lines. The part dealing with water is especially good. Entirely complete from the chemical standpoint, it also includes a good brief description of the microscopical findings. The standard of pollution—excretal *B. coli* in 10 cc. quantities or less—is worthy of more attention than usually given it. The chapter on air is fairly complete, but a great deal might be added to make it more thorough. The subject matter of the section on milk does not impress one favorably. The



methods of analysis are different from those used in America and in our opinion inferior to them. The discussion of the examination of foods is more satisfactory and considerable attention is paid to lower animal and plant life deleterious to foods. This is a new phase of hygiene which requires more extensive investigation. Such subjects as "Preserved and Tinned Provisions," "Chemical Antiseptics and Tests for These," "Methods of Adulteration" and "Coloring Matters Added to Food" are briefly but capably presented. A discussion on disinfectants concludes the work.

*Practical Therapeutics.* By DANIEL M. HOYT, M. D. Cloth, \$5.00. (St. Louis: C. V. Mosby Company, 1914.)

The title is misleading. The book contains no systematic consideration of the treatment of diseases; symptomatic therapeutics is its keynote. "New and Non-Official Remedies" of the Council of Pharmacy of the American Medical Association is included and constitutes the most valuable part of the work.

*Practical Therapeutics.* By HOBART AMORY HARE, M. D. (Philadelphia: Lea & Febiger, 1914.)

That 15 editions of Hare's *Practical Therapeutics* have appeared in 24 years is sufficient to show that the book is meeting a distinct need in American medicine. It is probably the most comprehensive and most useful one-volume work on practical therapeutics of American authorship.

*Child Training as an Exact Science.* A Treatise Based upon the Principles of Modern Psychology, Normal and Abnormal. By GEORGE W. JACOBS, M. D. With illustrations. (New York and London: Funk & Wagnalls Co., 1914.)

This book, written for the teacher and educator, presents a plea for the training of the individual child according to his needs, rather than for the training of children *en masse*, as now practised in schools. The historical portion of it seems better fitted for the physician and student than for the teacher, who may not be interested in the ups and downs of the education of the feeble-minded with its disappointments and failures up to the time of Séguin. The book is based upon the assumption that every organ of the body has a relation to mental function. The author devotes several chapters to the "Psychology of Childhood," in which he describes first the organs of mental activity—in other words its machinery—and later the steps in the intellectual development of the child. Then follows an account of the psychic abnormalities of the child, whether produced by organic defects, like cretinism, adenoids, imbecility or idiocy, or by functional disorders like hysteria, neurasthenia and the various phobias which weaken the will.

Another section of the book treats of the prophylactic training of the parents, by means of which those suffering from constitu-

tional defects can be prevented by law from marriage or procreation—an impossible task; and of a similar training of children by the use of wise pedagogic methods, nutritious food, gymnastic exercises, manual instruction, kindergarten occupations, Montessori methods and finally sympathetic efforts to form the will and character.

The final section treats of what the author terms the therapeutic treatment of defective children, who, although "burdened," are educable, and also of the uneducable. The book will do good and ought to be read by parents and teachers. It is well illustrated and attractively printed, although disfigured by minor attempts at advanced spelling.

*Ionic Medication.* By H. LEWIS JONES, M. D. Cloth, \$1.50. (Philadelphia: P. Blakiston's Son & Co., 1914.)

Dr. Jones attempts to give a "fairly complete record of the actual clinical results which have up to now been gained from ionic medication." The book impresses one as having been compiled by an enthusiast, who is a special pleader. It does not present sufficient proof of the value of ionic medication in any one disease, or in the relief of any one particular symptom, to engender in the reviewer much enthusiasm for the method.

*The Principles of Pathologic Histology.* By FRANK B. MALLORY, M. D. Cloth, \$5.50. (Philadelphia: W. B. Saunders Company, 1914.)

The book contains many admirable features. In the arrangement of the subjects discussed the author follows the usual form except as regards the chapter on "Special Injurious Agents and the Lesions they Produce." In this chapter the different disease-producing agents are taken up and the effect of each upon the body and the different organs of the body is discussed in full. The advantage of this feature is quite distinct. Another important change is the introduction of a new classification of tumors, which renders the subject much more clear and comprehensible. The inclusion of the leukæmias and of Hodgkin's disease under this head, however, is open to discussion, more especially in the light of our present knowledge of the latter disease.

Throughout the book, the text is clear and concise. The introduction of the term "endothelial leucocyte," applied to a type of cell, and its application throughout the book to a class of cells are apt to lead to some confusion. In many instances where there are divergent views on certain points, Dr. Mallory has given the one that he considers to be correct, but neglects to mention the opposing views. This, and the fact that practically no references are given to the literature on the subjects discussed, make the book rather a monograph than a text-book.

The illustrations are wonderful and add greatly to the attractiveness of the volume. As a whole, Dr. Mallory's book is a great addition to the literature on pathology.

## BOOKS RECEIVED.

*Obstetrical Nursing.* By Charles Sumner Bacon, Ph. B., M. D. Illustrated with 123 engravings. 1915. 12°. 355 pages. Lea & Febiger, Philadelphia and New York.

*Diseases of the Bronchi, Lungs and Pleura.* By Frederick T. Lord, M. D. Illustrated with 93 engravings and 3 colored plates. 1915. 8°. 605 pages. Lea & Febiger, Philadelphia and New York.

*Infant-Feeding. Its Principles and Practice.* By F. L. Wachenheim, M. D., 1915. 12°. 340 pages. Lea & Febiger, Philadelphia and New York.

*Student's Manual of Gynecology.* By John Osborn Polak, M. Sc., M. D., F. A. C. S. Illustrated with 100 engravings and 9 colored plates. 1915. 12°. 414 pages. Lea & Febiger, Philadelphia and New York.

*Quain's Elements of Anatomy.* Eleventh edition. Editors, Sir Edward Albert Schafer, LL. D., Sc. D., M. D., F. R. S., Johnson Symington, M. D., F. R. S., and Thomas Hastie Bryce, M. A., M. D. In four volumes. Vol. IV. Part I. *Osteology and Arthrology.* By T. H. Bryce. With 247 text figures and 28 colored plates. 1915. 8°. 329 pages. Longmans, Green & Co., London, New York, Bombay, Calcutta and Madras.



*The Alimentary Tract. A Radiographic Study.* By Alfred E. Barclay, M. A., M. D., B. C. (Cantab.), M. R. C. S., L. R. C. P. 1915. 8°. 195 pages. The Macmillan Company, New York.

*United States Army. Index-Catalogue of the Library of the Surgeon General's Office, United States Army. Authors and Subjects. Second Series. Vol. XIX. U.—UZZIELLI.* 1914. 4°. 674 pages. Government Printing Office, Washington.

*Nursing and Care of the Nervous and the Insane.* By Charles K. Mills, M. D. Third edition. Revised by the author, assisted by N. S. Yawger, M. D. 1915. 12°. 142 pages. J. B. Lippincott Company, Philadelphia and London.

*The Commoner Diseases. Their Causes and Effects.* By Dr. Leonhard Jores. Authorized English translation by William H. Woglom, M. D. With 250 figures in the text. 1915. 8°. 424 pages. J. B. Lippincott Company, Philadelphia and London.

*Differential Diagnosis. Volume II.* Presented through an analysis of 317 cases. By Richard C. Cabot, M. D. Profusely illustrated. 1915. 8°. 709 pages. W. B. Saunders Company, Philadelphia and London.

*Dissection Methods and Guides.* By David Gregg Metheny, M. D., L. R. C. P., L. R. C. S. (Edin.), L. F. P. S. (Glas.). Illustrated. 1914. 8°. 131 pages. W. B. Saunders Company, Philadelphia and London.

*A Laboratory Manual and Text-Book of Embryology.* By Charles William Prentiss, A. M., Ph. D. With 368 illustrations, many of them in colors. 1915. 4°. 400 pages. W. B. Saunders Company, Philadelphia and London.

*A Practical Text-Book of Infection, Immunity and Specific Therapy.* With Special Reference to Immunologic Technic. By John A. Kolmer, M. D. With an introduction by Allen J. Smith, M. D., Sc. D., LL. D. With 143 original illustrations, 43 in colors. By Erwin F. Faber. 1915. 8°. 899 pages. W. B. Saunders Company, Philadelphia and London.

*A Text-Book of Diseases of the Nose and Throat.* By D. Braden Kyle, A. M., M. D. With 272 illustrations, 27 of them in colors. Fifth edition, thoroughly revised and enlarged. 1914. 8°. 856 pages. W. B. Saunders Company, Philadelphia and London.

*Diagnostic and Therapeutic Technic.* A Manual of Practical Procedures Employed in Diagnosis and Treatment. By Albert S. Morrow, A. B., M. D. With 860 illustrations, mostly original. Second edition, thoroughly revised. 1915. 8°. 834 pages. W. B. Saunders Company, Philadelphia and London.

*Cancer: Its Cause and Treatment.* By L. Duncan Bulkley, A. M., M. D. 1915. 12°. 230 pages. Paul B. Hoeber, New York.

*Nature and Nurture in Mental Development.* By F. W. Mott, M. D., F. R. S., F. R. C. P. With diagrams. 1915. 12°. 151 pages. Paul B. Hoeber, New York.

*The Difficulties and Emergencies of Obstetric Practice.* By Comyns Berkeley, M. A., M. D., M. C., Cantab., F. R. C. P., Lond., M. R. C. S. Eng., and Victor Bonney, M. S., M. D., B. Sc. Lond., F. R. C. S. Eng., M. R. C. P. Lond. Second edition. With 302 illustrations. 1915. 8°. 807 pages. P. Blakiston's Son & Co., Philadelphia.

*Diseases of the Skin.* By James H. Sequeira, M. D. Lond., F. R. C. P. Lond., F. R. C. S. Eng. Second edition. With 48 plates in color and 238 text figures. 1915. 8°. 650 pages. P. Blakiston's Son & Co., Philadelphia.

*Diabetes Mellitus.* By Nellis B. Foster, M. D. [1915.] 8°. 243 pages. J. B. Lippincott Company, Philadelphia and London.

*International Clinics.* A Quarterly of Illustrated Clinical Lectures and Especially Prepared Original Articles. By leading members of the medical profession throughout the world. Edited by Henry W. Cattell, A. M., M. D. Volume I. Twenty-fifth series. 1915. 8°. 303 pages. J. B. Lippincott Company, Philadelphia and London.

*Progressive Medicine.* A Quarterly Digest of Advances, Discoveries and Improvements in the Medical and Surgical Sciences. Edited by Hobart Amory Hare, M. D. Assisted by Leighton F. Appleman, M. D. Volume I. March, 1915. 8°. 382 pages. Lea & Febiger, Philadelphia and New York.

*Cystoscopy and Urethroscopy.* By Bransford Lewis, B. S., M. D., F. A. C. S., and Ernest G. Mark, A. B., M. D., F. A. C. S. With a chapter by William F. Braasch, M. D. With 113 illustrations, 23 of which are printed in colors. 1915. 8°. 238 pages. P. Blakiston's Son & Co., Philadelphia.

*Transactions of the New York Surgical Society.* Volume II, 1913. Edited by William C. Lusk, M. D. 1914. 8°. Published by Annals of Surgery, Philadelphia.

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# BULLETIN

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## THE RELATION BETWEEN CLINICAL AND LABORATORY DATA IN TUBERCULOSIS.\*

By ALFRED H. CAULFEILD, M. B.

(Department of Medical Research, University of Toronto.)

Unforeseen interruptions in our work must be my apology for the incompleteness of this paper. Since August, 1914, we have been able to undertake very few new cases, and have made very few further observations on our old cases, so that at present I have only a few data to present in addition to those which we published in July in the Transactions of the tenth annual meeting of the National Association for the Study and Prevention of Tuberculosis. During that month we had started a card index of the cases in which the laboratory results had aided us in forming a more definite opinion than might have been possible by clinical methods alone. This was done merely that we might be more certain of keeping in closer touch with the subsequent history of these patients, as they seem to drift about and easily get out of reach. Unfortunately it has been impossible to keep this up to date and the partial report which

one of the visiting nurses was able to get in December leaves out a great deal that was essential. Under these circumstances I thought a very fair method of checking the value of the work would be to give the subsequent history of those cases published as typical examples in July.

We have sought to show a correlation between certain laboratory results and the clinical course of tuberculosis by performing these reactions in a more or less routine fashion upon the patients presenting themselves at the Tuberculosis Clinic of the Toronto General Hospital, and also upon certain patients sent us for this particular purpose. All told, very nearly 500 cases have been investigated in this fashion, although, as the work has now been twice interrupted, the number which has been followed consistently is greatly under this figure. I should add, perhaps, that in tuberculosis cases showing changes will be found only by following a large number of patients for a comparatively long period of time. It is of

\* Read before the Laennec Society, Johns Hopkins Hospital, January 25, 1915.



course this necessity of following a large number of cases in order to demonstrate a few instances of marked correlation between the laboratory results and the comparatively sudden change in the clinical course that makes the work long and tedious.

The two means of obtaining data to which I will refer as laboratory methods to-night have been:

(1) Estimation of tuberculin sensitiveness (or hypersensitiveness).

(2) Test-tube reactions with the patient's serum—an alcohol-ether extract of *B. tuberculosis*, as antigen, and an ordinary hæmolytic system, such as is used for complement fixation, being employed.

These test-tube results divide themselves into three end-reactions as follows:

- (a) Inhibitive reaction.
- (b) Fixation reaction.
- (c) Indifferent reaction (negative).

This is a sort of modification and enlargement of the Bordet-Gengou complement-fixation phenomenon and I might explain the nomenclature by quoting from previous papers on this method:

The technique adopted to demonstrate the different end-results, which in the case of the inhibition reaction is a phenomenon the reverse of true complement fixation, is based upon the fact that all antigens are capable of non-specifically absorbing complement in various degrees. Now, if to an appropriate series of antigen dilutions, whose complement-absorbing capacities are quantitatively shown, sera are added, it will be found that the serum may show any of the following results:

(1) True complement fixation (the demonstration of this taking place in antigen dilutions which absorb only minimal parts of a unit of complement).

(2) Indifferent result (the addition of serum does not affect the quantity of complement absorbable by the same amount of antigen by itself).

(3) Inhibitive reaction (this serum so reacts with antigen that, in contrast to the same amount of antigen by itself, it absorbs less complement. Naturally then the different end-results are quantitative and must be so read).

The estimation of tuberculin sensitiveness has been made by using a definite quantity of tuberculin cutaneously and latterly intra-cutaneously (the von Pirquet and Mantoux methods), and recording the degree by measuring the result. These data showing that the tuberculin sensitiveness varies very markedly during the course of the disease is also supplemented by similar results in clinically non-tuberculous persons. So far as I have noticed, ours is the only report showing such a curve for the latter, although many others have also shown this in the tuberculous, a recent paper being one by James B. Holmes. In a previous report we have shown curves of the tuberculin sensitiveness in both the tuberculous and non-tuberculous that represent a duration of four to five years. One great difference in the curves that we have thus obtained and those published by others lies in the fact that our estimations have been made at such long intervals that it was impossible

for the previous use of the tuberculin to affect the subsequent result, which might have been a theoretical contention.

Generally speaking, patients whose sera give an inhibitive reaction are doing well at the time. This seems more marked when their tuberculin sensitiveness (hypersensitiveness) is either very marked or very slight. Not all patients whose sera give the indifferent (negative) result are retrogressing, but they usually are, or are remaining *in statu quo*. Again, all patients whose sera maintain the complement-fixation result seem to go rapidly backwards. I should add that of the 14 persons in whose sera this latter reaction has been found only one, so far as we know, has continuously maintained it. Apart from this general correlation the most noticeable fact is that when a marked change in the test-tube result with a patient's serum is demonstrated, this is nearly always followed by a change in the clinical course. I say nearly always, because it is not always possible to be quite certain of this clinically, while again a subsequent test of the serum may give the original reaction. These test-tube results vary quantitatively, and one may be in doubt if the change is a marked one.

Having briefly outlined the type of the laboratory and clinical correlation, I shall now proceed to deal with these subsequent histories, and then attempt to outline the further researches which I now hope we shall be able to finish.

#### RESULTS OBTAINED ON CLINICAL NORMALS.

Work with this material was being continued because we believe tuberculin sensitiveness and the test-tube serum reactions result from tuberculous infection. Normals must every now and then fail to become clinically tuberculous, because they successfully resist implantations or reactivation, and not because these events do not happen. We had hoped that, if a sufficient number were followed in this way, variations would be found and possibly a correlation obtained. In the list of 18 cases so observed four gave variations. The variations obtained in one of these cases (No. 4) led to a gradual suspicion of tuberculosis which was confirmed clinically and bacteriologically. This patient, without entirely stopping his work, has remained free from any marked clinical evidence of the disease, and, although now lost to observation, is known to be well and working; indeed, he has never ceased work. Case 2 showed the most marked variations during 1910 and 1911, when clinical tuberculosis was suspected, but not confirmed. Since then the variations have ceased, and at present there have been no symptoms suggesting tuberculosis. Of the two remaining cases one (No. 12) complained at the time of the variations of definite discomfort in his knee. This has since disappeared. No further observations have been made, so that any discussion could be only theoretical, and would bring up the possibility of the tubercle bacillus as a possible cause of rheumatic-like complaints.

#### RESULTS OBTAINED IN CASES OF DEFINITE EXPOSURE.

Our purpose with this sort of material was to demonstrate the results which would be obtained in persons who had definitely been exposed, and in whom the exposure was followed



by no apparent clinical manifestations. If our theory were correct all, or nearly all, of these cases should show, as well as tuberculin sensitiveness, an inhibitive serum reaction.

Of the seven cases published all gave an inhibitive reaction, although in two it was not marked. One case cannot be traced; of the remaining six, none shows any evidence of tuberculosis. The tuberculin sensitiveness varied a good deal, as did also the probable duration of the exposure. In one case, where the exposure was intimate and of short duration, a rise in the tuberculin sensitiveness was shown following the exposure.

#### SUBSEQUENT HISTORIES OF CASES GIVING DOUBTFUL EVIDENCE OF PULMONARY TUBERCULOSIS.

The examples published were from a list of patients in whom a diagnosis of tuberculosis could neither be excluded nor confirmed with certainty by clinical methods. The logic of the laboratory results helping in a diagnosis lies in the value of marked changes being found in the reactions in repeated tests, especially if these correspond to changes in the clinical welfare, as we find they do, in the definitely tuberculous.

Five cases have been cited above as examples. In cases 1 and 2 tuberculosis was excluded by means of the laboratory results; both patients at present are alive and well and are working or are capable of doing so.

In Cases 3, 4 and 5 tuberculosis was diagnosed as being a cause of the clinical picture. Case 3 got worse and returned to Russia. Case 4 is now in the hospital and tuberculosis is only slightly more evident on physical examination than formerly, but no other diagnosis has been arrived at, nor have any further tests been made. In Case 5 we were searching for a differential diagnosis for masses which could be palpated in the abdomen. Tuberculosis was diagnosed and new growths were excluded. The enlargements are about the same and the patient is going to school at the present time.

At the time these five cases were selected as examples we had drawn up a much longer list, but thought five would be sufficient. One of those that would have served equally well as an illustration has shown such a marked change subsequently that I will now add this history (No. 2822) as a further illustration. On April 24, 1914, the diagnosis of tuberculosis was aided by the laboratory results and a further note of "apparent recovery" was added to the history. This patient, although told to report monthly or at any time he did not feel well, did not come to the clinic until November. He then gave a history of having felt sick for some time and his condition was found to have advanced to such an extent that an artificial pneumothorax was considered.

In this class of material I feel that the value of the methods is to be judged in two ways: (1) Of those cases in which we have excluded tuberculosis, after six months or more, a high percentage should still be clinically free. It is of course possible that subsequently a few may contract tuberculosis. (2) Of those patients in whom biologically active tuberculosis was diagnosed, a very high percentage should subsequently show definite tuberculosis.

#### SUBSEQUENT HISTORIES OF THE DEFINITELY TUBERCULOUS

To these cases which have been published there can, of course, be very little added. Some of the patients have remained *in statu quo*, others have shown progress or retrogression, but not many more observations have been made on these particular cases. Here again I do feel it essential that not only should there be examples in which the correlation is excellent, but that there should also be practically no instances in which the laboratory results, when taken with the apparent clinical findings, would have been misleading. In a few cases, in which the clinical course has not seemed to correspond as closely as could be desired with the indications given by the laboratory results, it has been difficult to decide whether the laboratory results were really to blame. Sometimes other complications have obscured judgment and sometimes the laboratory results, as shown by repetition, have altered. I can only state that, as far as we have been able to interpret the results, we have not been misled to any important degree. This work has included a great number of severe tests, as, for instance, the differential diagnosis in cases of suspected miliary tuberculosis. In this sort of material so far all our results have been confirmed by the post-mortem diagnosis.

From continued observation, utilizing both the two laboratory and the clinical findings, we have come to regard a marked inhibitive serum reaction as significant of high resistance to the tubercle bacillus, and particularly so if the tuberculin sensitiveness is either marked or minimal. Whether a marked inhibitive serum reaction can be found with a non-active tuberculosis cannot possibly be satisfactorily determined by observations on human beings. In fact the actual proof of the relation of tuberculin sensitiveness and the serum reaction to the clinical progress can only be proved by experimental work with animals, and it is the attempt that we are making in this direction that I will now try to outline.

Previous work with the small laboratory animals had failed to show any method of inoculation whereby the inhibitive reaction of the serum could be produced. When we were forced to give up the convenient guinea-pig and rabbit, cattle naturally suggested themselves, and in November, 1912, we collected samples of blood from different cattle, and at the same time made an intracutaneous or subcutaneous tuberculin test, or both. Thirty-two animals have been so examined and certain of these repeatedly tested. The results showed correlated data very comparable to those obtained with human beings. In only one instance did we obtain an indifferent reaction with an absolutely tuberculin-negative reaction. As the animal was an expensive thoroughbred at the Guelph Experimental Farm it was not autopsied. One animal, a Jersey cow, showed marked complement fixation on four different occasions between July and November, 1914. This cow retrogressed so rapidly from July that she had to be killed in November, and the autopsy showed very extensive tuberculosis. The tuberculin reactions had always been very marked. Moreover, this was the only animal that gave complement fixation, all the others showing



either the indifferent or various degrees of the inhibitive serum reaction. We have experimentally inoculated with living tubercle bacilli three healthy looking animals, each having shown a different set of laboratory results, and, to judge by the results after the use of the intracutaneous tuberculin test and the test-tube serum reactions, it is evident that following the inoculation different animals respond differently.

Encouraged by this we have produced also pleural exudates in certain of the inoculated animals and are attempting to determine whether it is possible that any immune substance may be present in either the blood serum or the pleural exudates of any of these animals, which under a similar inoculation have responded in an apparently different way biologically.

In closing I should like to refer to certain publications by Calmette,<sup>1</sup> in which he describes a reaction which he calls *inhibiteur*. Although there are differences in the technique and antigens, many of the conditions in which Calmette finds his inhibitive reaction are those in which, I believe, the reaction I have called "inhibitive" might also be found. This is particularly noticeable to me in one of his fuller communications.

#### DISCUSSION.

DR. HAMMAN: There are a number of interesting aspects from which Dr. Caulfeild's paper might be viewed. As regards the specificity of his test and its relation biologically to complement absorption and other serum reactions, only one actively engaged in studying these questions would be qualified to speak. Dr. Caulfeild has said that he is convinced from his results of the absolute specificity of the reaction and from the clinical standpoint the results of his work are of great interest. For many years we have looked to biological tests to help us in the diagnosis of tuberculosis and in its treatment. The many biological tests that have been tried have so far been of little clinical value. Precipitin reactions, agglutination reactions, opsonin reactions and complement fixation have all been tried on a large scale and though biologically their specificity may be certain, still clinically they have been of little value in the study of tuberculous disease. This is no doubt due to the complex nature of tuberculosis from the clinical standpoint, the complexity, I take it, consisting merely in this fact, that infection and disease in tuberculosis are not synonymous terms as they are in practically all other infections. It must be remembered that the tuberculin reaction is just as delicate and just as specific as the Wassermann reaction

<sup>1</sup> Calmette et Massol: Ann. Instit. Pasteur, 1914, XXVIII, 338.

and the reason it has less clinical value is because in the clinic we must separate tuberculous infection from tuberculous disease, whereas no such distinction is necessary in syphilis.

As regards complement fixation, I admit that I am particularly influenced by the work of Roemer when I say that it has been of as little value in the study of tuberculosis experimentally as it has in clinical studies. Roemer has tried out the test very thoroughly in animals and has found that there is no relation between the presence or absence or the degree of complement fixation and the severity and extent of the disease in animals, or of resistance to superinfection. I have myself come gradually to feel that immunity in tuberculosis is more closely bound up with hypersensitiveness than with any protective body or bodies in the serum. I realize that at present there is in some quarters a tendency to lay more emphasis than has recently been done upon the humoral aspects of immunity in tuberculosis.

I am particularly interested in what Dr. Caulfeild has said about the relation of his test to the tuberculin test. I understood him to say that in patients showing a well-marked reverse reaction the outlook was favorable, whether they reacted severely or mildly to tuberculin. We have been very much interested in the relation of tuberculin hypersensitiveness to prognosis in tuberculosis and we have opposed the attitude that is commonly accepted, namely, that the higher the degree of hypersensitiveness the more resistant the patients and the more likely they are to improve. Our work has convinced us that, other things being equal, those who have a low tuberculin hypersensitiveness are in a better way to recover than those in whom the hypersensitiveness is very high. This conclusion, however, is only relative, for at certain periods of the disease a high tuberculin sensitiveness may be associated with a very good prognosis. The question is complicated and I cannot go into it in detail. I wish merely to say that if Dr. Caulfeild's reaction will tell us which patients are likely to do well, whether they have a high or a low tuberculin hypersensitiveness, it will prove to be a very valuable clinical aid in our study of the disease.

DR. CAULFEILD: Dr. Hamman has touched on two very important features. I feel very strongly myself that we shall not get any one serological reaction which is going to be pathognomonic of the disease. Therefore, one must get a combination of serological or biological results which will outline the patient's resistance. That is what I have been more or less hoping.

Dr. Hamman speaks about tuberculin hypersensitiveness and lack of hypersensitiveness. I always have felt that, because of the correlation between the two groups, one very often gets in an absolutely clinical normal a very high degree of tuberculin sensitiveness, which must indicate that that patient has successfully resisted tuberculosis.

## SOME CULTURAL STUDIES ON THE TUBERCLE BACILLUS.\*

By S. A. PETROFF,

*Adirondack Cottage Sanitarium.*

More than thirty years have passed since Koch discovered the tubercle bacillus. By infecting guinea-pigs with tuberculous material he was enabled to cultivate from the spleen the organism in serum media. It took eight weeks, however, for the growth to appear. At that time the tubercle bacillus could be isolated in only one way—through infected tissues. In 1909 Uhlenhuth and Kersten, in a report on the bactericidal action

exerted by antiformin on many organisms, called particular attention to the fact that it had little or no effect on the tubercle bacillus. The same authors were the first to isolate and cultivate the organism by the aid of this compound. Dr. Lawrason Brown, at the Adirondack Cottage Sanitarium, modified somewhat their method and, with Smith, reported the successful isolation and cultivation of tubercle bacilli from forty-five sputa. Some later workers, following their method, failed to cultivate *B. tuberculosis*, but the failure was due not to the

\* This investigation was made possible by the Harriman-Sage Fund. Paper read before the Laennec Society, January 25, 1915.



method, but to faulty technique. A 30 per cent antiformin was used, a solution of fairly high specific gravity. Equal parts of 30 per cent antiformin and sputum were shaken well and incubated. The sediment was then washed with sterile water and again centrifugalized. This procedure was repeated. At times the method was very effective, but did not prove of great practical value on account of the elaborate technique involved. In repeated washings, many of the organisms were not thrown down; in many instances we have found tubercle bacilli on the surface, some in the fluid and some in the sediment; moreover, the possibility of contamination was great. Repeated trials to apply this method to cultivating the tubercle bacilli from the feces failed to give a positive growth free from contaminating organisms. In the spring of 1914, at the suggestion of Dr. Lawrason Brown, we started this investigation from the point where he had left off, and without his hearty co-operation this work could not have been so successfully accomplished.

The effect of certain aniline dyes on the development of the bacterial cell was known even in 1886, when the botanist Pfeiffer demonstrated the harmful effect of these dyes upon higher plants. Rozsahegyi pointed out their effects upon different bacteria, and these pioneers were followed by Cornil, Babès, Penzoldt, Stilling and many others, who published very interesting results of investigations, although none of them appreciated the connection between these properties of the dyes and their practical application in bacteriology. Churchman was the first, to my knowledge, to study this subject systematically and in the course of his work made a very practical discovery. It was the work of Churchman, followed by that of Simons and other investigators, which suggested the use of aniline dyes in the isolation of the tubercle bacillus.

After it had been demonstrated that tubercle bacilli would grow in a medium containing gentian violet 1 to 50,000, an attempt was made to cultivate them directly from the sputum. Only a few Gram-positive organisms appeared in the tubes. Of these organisms some were staphylococci and others streptococci. They were carefully studied. Gentian violet does not possess properties inhibitory to these organisms even in a dilution of 1 to 1000. For the elimination of them several alkalies with bactericidal properties were studied. In selecting the alkali we tried to find one that could be easily neutralized, bearing in mind that the resulting salt must not affect the tubercle bacilli. Sodium hydroxide proved of value. But before proceeding we carried out a small experiment on the bactericidal action on tubercle bacilli exerted by this alkali. A 4 per cent solution of sodium hydroxide will not destroy the tubercle bacillus when incubated at body temperature for 24 hours, and, as this alkali possesses a high bactericidal property against all streptococci and staphylococci, it was selected.

The next step was to determine what dilution of gentian violet was most favorable for the development of the tubercle bacillus. A series of media containing different dilutions of gentian violet, varying from 1 to 1000 to 1 to 100,000, was used. A dilution of 1 to 10,000 gave the best results.

In my last communication, in the Journal of Experimental Medicine for January, 1915, may be found the details of all

this work. Here I shall give very briefly the preparation of the medium and also the method of isolating and cultivating the organisms from the sputum and the feces.

After many trials it was found that a medium containing whole egg, beef or preferably veal juice and gentian violet gives uniformly positive results. This medium contains: One part of meat juice, two parts of the egg (white and yolk), gentian violet sufficient to make a solution of 1 to 10,000.

I. *Meat Juice*.—Five hundred grams of beef or veal are infused in 500 cc. of a 15 per cent solution of glycerine in water. Twenty-four hours later the meat is squeezed in a sterile press and the infusion collected in a sterile beaker.

II. *Eggs*.—Sterilize the shells of the eggs by immersion for ten minutes in 70 per cent alcohol or by pouring hot water upon them. Break the eggs into a sterile beaker and after mixing well, filter through sterile gauze. Add one part by volume of meat juice to two parts of egg.

III. *Gentian Violet*.—Add sufficient 1 per cent alcoholic solution of gentian violet to make a proportion of 1 to 10,000.

After mixing well for a few minutes the medium is tubed as usual and inspissated for three successive days, first at 85° C., until all the medium is solidified, and on the second and third days for one hour at 75° C. Lately we have found that even a temperature of 100° C. will not decrease the nutritive properties of the medium.

We have noticed a great variation in the gentian violet, that is, some samples gave a deeper color to the medium than others. This variation we cannot at this time explain.

#### METHOD OF ISOLATING TUBERCLE BACILLI FROM THE SPUTUM.

To obtain rapid and uniform results, fresh sputum must be used. Equal parts of sputum and 3 per cent sodium hydroxide are shaken well and incubated at 38° C. for from 15 to 30 minutes, the time for incubation depending on the consistency of the sputum. This mixture is then neutralized to litmus paper with hydrochloric acid and centrifugalized at high speed for 10 minutes, the supernatant fluid is decanted and the sediment inoculated into the medium described above.

We have controlled the gentian violet medium with one made of an egg and meat juice only. Many of the tubes containing the plain medium were contaminated, and the contaminating organism was mostly *B. subtilis*. On the other hand, the gentian violet medium was free from these contaminating organisms. Occasionally we have met with some molds which are not inhibited by the gentian violet.

#### METHOD OF ISOLATING TUBERCLE BACILLI FROM THE FECES.

It is an entirely different problem to isolate and cultivate tubercle bacilli from the feces. Here we have many spore-forming organisms which resist the action of sodium hydroxide. Here the time of incubation plays a more important part than the concentration of sodium hydroxide. Feces are collected in wide-mouthed jars, a fresh morning specimen giving the best results. The feces are diluted with three volumes of water, mixed well and then filtered through several thicknesses of



gauze to remove solid food particles. The filtrate is saturated with sodium chloride and left undisturbed for a half hour. At the end of that time all bacteria will be found floating. This floating film is collected with a deflagration spoon in a wide-mouthed bottle, and an equal volume of normal sodium hydroxide is added. This is shaken well and left in the incubator, at 38° C., for three hours. It should be shaken every half hour, neutralized to sterile litmus paper with normal hydrochloric acid, centrifugalized, and the sediment inoculated into the several tubes containing the medium.

The appearance of the growths was not uniform. In the case of the sputum, in one instance we obtained a visible growth on the fifth day, but in others the growth was not seen until the 14th or 15th day. The average time for the appearance of a visible growth was nine or ten days. By close observation, we noticed that the moisture of the medium influenced to some extent the development of the organism. At the present time, it is our routine, after inoculation, to leave the tubes in the incubator for a few days, until the moisture carried from the centrifuge tubes is completely absorbed by the medium, or evaporated. Then the tubes are paraffined to prevent the further drying of the medium.

The temperature of the thermostat is of considerable importance. A constant temperature of 38.5° C., is most suitable for the rapid growth of the tubercle bacillus.

The growth from the feces appeared much more slowly than that from the sputum. On an average from two to three weeks elapsed before the growth was perceptible. In all probability many of the tubercle bacilli are dead or weakened when passed with the feces.

A study was carried out with glycerine-agar and egg-meat-juice media, for the purpose of observing the differences in cultural characteristics on the two media. A series of tubes of these two media, containing gentian violet in the proportion of 1 to 10,000 to 1 to 100,000, was used. Several distinct types were inoculated in the usual way and incubated. The growth in the egg medium was abundant at the end of the fifth day, whereas the agar cultures gave a scant growth. Some of the strains decolorized the agar as well as the egg medium, while in others, which did not develop so rapidly, the growth appeared in the tubes to be stained violet. Upon microscopical examination of the latter strains, however, only a few of the organisms were found to have absorbed the stain. Most of the dye appeared to be adherent to the bacterial cell and subcultures gave no positive growth. Churchman, in studying *B. typhosus* on gentian violet media, observed the same phenomenon, but on subculturing he obtained an abundant growth. *B. tuberculosis* will not continue to grow on gentian violet media and all subcultures after isolation must be carried on in a dye-free medium. Only a few types of tubercle bacilli will grow in glycerine-agar-gentian-violet media. When grown upon media containing the dye, a type that decolorizes the media is of longer life than one which has selective properties for the dye. What the factors are which bring about the decolorization of the media we are not at present able to state.

A comparative study was also carried out with methylene blue. The dye has no influence upon the growth of the tubercle

bacillus in a dilution of 1 to 100,000. The growth appears the same as on a dye-free medium. Upon microscopic examination we find that the dye adheres to only a few bacterial cells. When we use this dye in the proportion of 1 to 50,000 the growth seems to be retarded for several days. The whole mass used for inoculation appears to be blue. Upon microscopic examination we find that a good many of the organisms have absorbed the dye. If we examine the tube a week later we find that the primary inoculation is still blue, while the medium surrounding and below this area is considerably decolorized and there is marked evidence of a new growth. This new growth does not appear to be blue, but upon microscopical examination we find many of the individual organisms stained in different shades of blue, some darker than others. Is it possible that, when the bacterial cell absorbs the stain, it is not killed, but simply that the process of reproduction is retarded for a while and then, when it divides into twos or threes, on account of the division, the staining is much lighter? Possibly other explanations may be offered; that the dead organisms are stained dark blue; that the light ones are not dead, and that after absorbing more dye they are killed. This phenomenon is under consideration and further investigation may throw some more definite light on the problem. The growth is completely inhibited if the medium contains the dye in the proportion of 1 to 25,000. The bacterial cells are uniformly stained very dark blue.

It is probable that there is more than one type of human tubercle bacilli. Out of 129 strains thus far isolated, we have noticed the occurrence of several apparently distinct types of organism, which may possibly be differentiated by their cultural characteristics. In some we have small pin-point colonies, which always give a scant growth on sub-culturing (this particular strain is one which has selective properties for the dyes), while others which decolorize the media produce long, spreading, veil-like, slightly raised colonies. The former type is slightly moist; the latter is dry.

Upon microscopical examination we find more striking differences. An organism that gives a very scant growth when stained by the Ziehl-Neelson method appears in minute rods, strongly resisting acid-alcohol decolorization. Granules could not be demonstrated. If we examine this type by the Gram method we find all to be in rod form.

On the other hand, if we examine a strain that gives a rapid growth we find a different picture. Stained by the Ziehl-Neelson method, only a few solid, slender, long granular rods are seen. The granules may be seen lying in the rods, sometimes close together like a string of beads, but most often separated by regular intervals. No isolated granules could be seen. The granules are only weakly stained and vary in size. By the Gram stain the preparation shows almost all the organisms in the form of granules; only an occasional solid rod. Numerous rows of granules are imbedded in a Gram-stained shadowy substance. Many single isolated granules of various sizes lie in orientation form. However, there are more than two strains, as I have already stated above.

Up to the present time we have been able to isolate and cultivate the tubercle bacillus from 129 sputa out of 135 specimens.



The method of isolation and cultivation has proved of some value in feces, as we can obtain a positive growth long before the infection is manifested in guinea-pigs. We hope to be able to use this method for isolating the tubercle bacillus from the urine.

The content of fatty acids present in tubercle bacilli, which varies greatly in different types, must, I believe, have some influence upon the virulence of the organism. At present, work is in progress upon the fatty acid content of different types, their cultural characteristics, tinctorial reactions and virulence to guinea-pigs, with the hope that it may lead to a classification of human tubercle bacilli.

In May, 1913, I reported before the National Association for the Study and Prevention of Tuberculosis a new fluid medium for the cultivation of tubercle bacilli.

Last summer I modified the medium to some extent, which made it give even better results. Briefly, I will describe the preparation of this new medium:

Five hundred grams of grated potatoes are infused in 1000 cc. of distilled water for 24 hours in the ice-chest. At the end of that time the infusion is filtered from the pulp through gauze, titrated and the reaction adjusted to 1 per cent acid. The filtrate is then heated in an Arnold sterilizer for one-half hour, until all the starch is coagulated, and then filtered through cotton. The pulp is then washed in a gauze bag under running water until free of starch (iodin test) and added to the filtrate separated from the coagulated starch, mixed well and put in the autoclave under 15 pounds pressure, filtered through filter-paper and titrated again. The final acidity must be between 0.5 and 1 per cent to phenolphthalein. Put 50 cc. in flat bottles holding 250 cc. and sterilize in the autoclave at 15 pounds pressure for half an hour. When glycerine is used in the medium, it must be sterilized in an Arnold sterilizer on three successive days. In this medium the tubercle bacilli will grow well, not only on the surface, but also in the depths of the medium.

When tubercle bacilli are grown on this medium they show marked variations; some grow in a veil form, while others will be found, as it were, piled one on top of the other. With some types many acid-fast properties are lost and after a while they will not continue to grow upon sub-culturing. It is possible that potato broth prevents to some extent the synthesis of fat present in the tubercle bacillus and that the protein is not affected.

Last summer at the suggestion of Prof. Zinsser, of New York City, a study of the antigenic properties of the growths of tubercle bacilli in this medium was undertaken and there is an

indication that this line of study may be of some value in relation to complement fixation in tuberculosis. However, the work, though promising, has not as yet progressed far enough to warrant a definite conclusion.

#### DISCUSSION.

DR. BARKER: I think we too often harbor the idea that the technique of bacteriology is a finished subject; that there is very little to add to it. But an instance such as this described by Mr. Petroff to-night actually represents an important step forward in technique. Koch's method of isolation by plating was a fundamental contribution to the science of bacteriology, but this method of obtaining a pure culture may be an onerous business in the case of certain bacterial mixtures, and it is no wonder that bacteriologists soon tried to find shorter cuts to pure cultures. One example of a "short cut" was the "method of enrichment" devised by Schottmüller for isolating the cholera bacillus. Later examples grew out of attempts to isolate the typhoid bacillus. We all know how hard it was formerly to get pure cultures of typhoid bacilli from the feces. As bacteriological technique gradually evolved, however, it was discovered that to our media could be added certain things which would favor the growth of the typhoid bacilli or which would inhibit the growth of other bacteria in the feces.

As regards pure cultures of *B. tuberculosis*, we were helped first by isolation through animal inoculation, and later, still further by the antiformin treatment of suspected material. Now Mr. Petroff has given us a method, somewhat complex as described, but quite practical, I imagine, on application. The previous evolution of cultural technique was largely along one line, the effort being made to kill all organisms except the one to be isolated. Formerly it took from three to four weeks to obtain a culture of the tubercle bacillus. By this method of Mr. Petroff's we learn that they may sometimes be grown in as short a period as five days. The method would seem to be valuable for diagnostic purposes and we expect to apply it here in special cases.

Another thing that interested me in Dr. Petroff's paper was the fact that we now have the means of obtaining quickly a large number of pure cultures of *B. tuberculosis* from different cases, and may therefore enter upon the task of differentiating different strains. It may be that the human type of *B. tuberculosis* is no unity. When we think of what happened in the study of the streptococci, for example, it would not surprise us to find several different strains of human tubercle bacilli. You remember that it was believed at first that there was only one typhoid fever and that it was due to the typhoid bacillus; now we know that there are several typhoid fevers, at least four, those due respectively to *B. typhosus*, *B. paratyphosus* alpha and beta, and *B. mandschuricus*. It is probable, too, that several different strains of the diphtheria bacillus exist. That such special differentiations of strains of a bacterial species may not be unimportant for diagnosis and even for prognosis and therapy seems to be demonstrated by the interesting studies of Neufeld, and of Cole and Dochez, on the pneumococci of lobar pneumonia.

## DIETL'S APHORISMS ON PHLEBOTOMY.\*

By NORMAN B. GWYN, M. D., Philadelphia.

While searching for some references upon "bleeding in pneumonia" I was confronted with the familiar name of Dietl—Joseph Dietl, of Vienna and Cracow—and found under it a

long monograph, "Der Aderlass in Lungenentzündung." The 102 clinical aphorisms with which this monograph terminates form the subject matter of my paper.

"Der Aderlass" seemed to have helped to make Dietl's reputation long before his accurate description of floating kid-

\* Read before the Book and Journal Club of the Medico-Chirurgical Faculty of Maryland, November 17, 1914.



ney's and the crises which bear his name. It is generally referred to as one of his chief contributions to the medical sciences and one naturally wondered, after glancing at his tables of 380 cases, if there might not be in 102 conclusions much that, at least, was interesting.

And interesting, indeed, I found them. Hippocratic at times in their truth and brevity, "Schlecht ist es wenn der Puls schon nach der ersten Venesection frei wird," might well have come from the great collection of aphorisms; while "Es gibt Pneumonien ohne Husten," "Es gibt keine chronische Pneumonien," "Die besten Pneumonien sind die bei denen nur wenig expectorirt wird," must satisfy the most vacillating student.

My interest waned somewhat on observing the date, 1848, twenty years after Louis; but the Cracow societies were still debating the "bleeding in pneumonia." Louis was still showing an affection for early bleeding and tartar emetic, and I felt, moreover, that the observations of one who at that early date could have the courage to carry through 189 cases of pneumonia, on dietetic measures alone, must not only be of interest, but of real value.

As far as one can judge, Dietl advances his arguments against blood-letting quite as if Louis' great protest had never been made. Dietl's methods are nevertheless Louis' methods—careful clinical observations ending in accurate statistical details. One senses an imitation, but hopes that the omission of any reference to Louis' work is accidental. Andral receives recognition in a reproof for his bloodiness; Laennec is completely ignored.

Dietl, as he says in his preface, had belonged to those "Streng Antiphlogistiker" who still saw in the then bloody treatment of pneumonia their greatest triumph. Seventeen years previously, however, some taint of heresy had crept into his mind, for in 1831-3 he had tried treating severe cases of pneumonia homeopathically—"Aber es fehlte mir jedoch der Muth den natürlichen Verlauf der Krankheit ruhig abzuwarten: Mit der Zunehmenden Athemlosigkeit und Angst des Kranken stieg auch die Meinige so hoch, dass ich in mitten der präsumptiven Arzneiwirkung reuig nach der Lanzette griff, und, da diese in den meisten Fällen Erleichterung brachte, wieder zur alten Fahne schwur, der ich nun fester anhing als je."

Clinging more firmly than ever he must have remained for nearly ten years, for his *Bezirks-Krankenhaus* appointment in 1841 found him "bleeding industriously."

Bleeding, however, had a rival. For many years Tartarus stibiatus had "proved itself" with the profession, and it was being found that in some cases one did not need to bleed if large doses of tartar emetic were given. The majority of teachers, even Louis, simply went from bleeding to antimony in 20 years. Dietl stepped from bleeding to large doses of tartar emetic with vomiting, from large doses with vomiting to small doses without vomiting, from small doses to no doses (an expectant treatment of pneumonia) at a revolutionary rate. Then followed three years' observation of pneumonia treated without bleeding, and, at the end of this period, was

put forth the "Aderlassung in Pneumonie," a protest larger at least and more elaborate than the great protest of Louis.

It is not my intention to review critically Dietl's monograph. It might be entertaining, for the indications of his later therapeutic nihilism are already apparent, but to most of us prolixity and a dogmatic positiveness would seem its chief characteristics; the carping reference to Andral is the only mention of any of the great teachers who had gone before him.

Almost every phase of pneumonia and the influence of bleeding upon it is taken up in the monograph; the aphorisms, of course, merely represent the crystallized result. Many have the stamp of originality, and their brevity and conciseness are attractive to a degree. They can possibly be presented more briefly and agreeably by using some reconstruction; Dietl's scheme in general can be easily followed; certain conditions of pneumonia are taken up, the application of bleeding considered, the probable or actual results detailed, and the dire effects of bleeding stated.

Not every aphorism pleases. I will try to put before you the more interesting and the most original:

#### ON THE PRODROMES.

The prodromes of pneumonia last longer in the young and strong, and those affected for the first time; they are shorter in the aged, weak, and those undergoing recurring attacks.

2. Venesection has the power to shorten the prodromal stages.

Dietl at no time denies that bleeding gives temporary relief.

#### ON THE DYSPNŒA SEEN IN THE EARLY STAGES OF PNEUMONIA.

The pneumonia patient breathes easier after completed hepatization than before.

The dyspnœa is not due to the filling of the lung cells with the plastic exudate.

Complete hepatization may limit the respiratory movements without bringing about respiratory distress.

The gaseous interchange in the lung cells is the ultimate inciter of the regulated activity of the nerve centers and the respiratory movements dependent thereupon.

On account of the enormous accumulation of fibrin as a protein-oxide a large amount of oxygen is withdrawn from the blood, and since there is reduction of the blood cells (the oxygen carriers) this, the oxygen, is never replaced in the same proportion.

12. In pneumonia less acid is taken out of the atmospheric air than is necessary for the oxidation of the venous blood and the vitalizing of the nerve centers.

13. The dyspnœa, then, must clearly be greatest during the period of the pouring out of the fibrin into the lung cells, since then the greatest call for, and the greatest deficiency of, oxygen is taking place.

15. The pneumonic's dyspnœa is preferably induced by altered chemical proportions of the blood.

17-18. Venesection should relieve dyspnœa by helping onward a continuous blood stream, more blood being driven through the capillaries in a given time, and (18) no other means of treatment suffices so to relieve dyspnœa, but (16) venesection brings about in the blood the same alterations as the pneumonic process (reduction of red blood cells and increase of fibrin), so that generally it must from chemical reasons rather increase than diminish dyspnœa.



## ON THE HEART.

23-24. The exudation process, the underlying disease itself, is the most probable cause of the increased pulse rate, rather than mechanical obstruction or the reduction of the red cells.

25. The pulse-rate drops after the venesection, but (26) the influence of venesection is usually only transitory and (28) can only occur if the individual is sufficiently full blooded.

31. In the unbled pneumonia there is seldom seen the same amount of cardiac disturbance as in the bled.

The tumultuous heart actions are in part consequences of the venesection.

## ON THE PULSE.

The indications for venesection were for the most part determined by the character of the pulse. The quiet, repressed pulse was considered favorable; the large, dicrotic, unfavorable, often seen in severe pneumonias and often bled for. To Dietl's mind the large pulse more regularly followed bleeding; to him it was a sure sign of increased serosity of the blood and asthenia; it was bad if it followed the first bleeding, and, further, he asserts that the return to a small normal pulse from a large dicrotic one was never so quick in the venesected cases as in those treated with dietetic measures alone.

The pulse of the pneumonias is dicrotic, but not completely so as in typhus.

The repressed pulse of the older pathologists is the normal and favorable; the large dicrotic is the abnormal and unfavorable of the various pulses of the pneumonias.

After single or repeated bleedings the pulse becomes large and dicrotic, it becomes "free," as one is accustomed to say; this "becoming free" of the pulse is a sure sign of increased serosity of the blood and asthenia.

It is bad if the pulse becomes free after the first bleeding.

In pneumonia treated by venesection, the large dicrotic pulse never returns so quickly to the normal as it does in those treated with dietetic measures alone.

## ON THE JAUNDICE SEEN IN PNEUMONIA.

Bilious pneumonias, our pneumonias with jaundice, were, by Dietl, seen to occur in direct proportion to the extent of the bleeding. Jaundice occurred but seldom in, and quickly disappeared from, the cases not molested with the lancet. On the other hand, it could be seen to deepen after each opening of the vein, and in many instances was directly produced thereby. To instance this:

The yellow color of the skin begins to decrease immediately after the completion of the exudate, and disappears within a very short time.

The yellow color of the skin occurs less often in the unbled cases.

The jaundice increases after each bleeding.

The jaundice is in many cases directly brought about by the bleeding.

It was interesting to note, in connection with the question of jaundice in pneumonia, that the pathologists of Dietl's time had recognized that obstruction of the large ducts and gross liver changes were not usually demonstrable in the fatal cases. To fasten the blame for the jaundice upon the bleeding would be Dietl's natural inclination in such cases, and in the substance of the monograph we find the following:

Venesection promotes excretion of and coagulation of the fibrin to a high degree, and from this comes an abnormal collection of pigment in the blood.

## ON THE SPUTUM.

That group of aphorisms which concern the sputum and the effect of bleeding upon its character makes one feel certain that Dietl must have been quite unacquainted with the work of either Laennec or of Louis, or that he willingly ignored both. He still busies himself with the venesection's power to produce the *sputa cocta* in the face of Laennec's clear description of the pneumonic expectoration, and his assault on bleeding is delivered at Andral, quite over Louis' shoulder, as it were: "Andral und andere Beobachtern die die Lanzette stets bei der Hand haben," Two of the aphorisms stand out:

The best pneumonias are those in which there is but little expectoration.

The *sputa cocta* are not a necessary product nor are they to be considered as a critical evacuation.

To these he adds the following:

It is a very favorable sign and one pointing to a quick resolution, if the expectoration ceases after completion of the exudate.

In the treatment of pneumonia by venesection the sputa undergo several alterations, among which is the transformation of the clear, tenacious expectorations into the so-called *sputa cocta*.

Venesection favors the breaking down of the pneumonic exudate into pus or pus-like cells, and indeed *sputa cocta* are often the product of venesection.

As we saw in Aphorism 2, Dietl was fair enough to give credit to bleeding for certain minor qualities; one other of these was its apparent power to relieve cough in the early stages.

Incontestable experience teaches that a single venesection will often lessen a cough or completely subdue it.

The short dry cough of pneumonia is due to the hyperæsthesia of the lungs.

The actual cause of the cough is a bronchitis.

Venesection lessens the cough by subduing the pulmonary hyperæsthesia and by diminishing the bronchial secretion; a similar mode of action is at work in the relieving of the dyspnoea.

Nihilism breaks forth in his declaration, "The expectant treatment has no remedy for the pneumonic cough."

Few of us realize how drastic the treatment of the disease could be before the various protestants had effected their reformation. The convalescence from any serious ailment must have been much prolonged; the critical resurrection of a pneumonia patient must have been often actually interfered with. Laennec realized this to a certain degree. Louis' arguments are always along rather different lines, and he could still see the marked improvement after the vomiting caused by the tartar emetic. Dietl would seem to strike here his highest note. From his aphorisms on this stage of pneumonia we may cite:

After the completed exudation in the unmolested pneumonia, the physiognomy expresses the highest degree of well being.

In the cases treated by bleeding this favorable change of the physiognomy does not show in so striking a manner, because the weakness induced by the bleeding does not leave the patient free to enjoy his return to well being.



In the expectant treatment the appetite returns immediately after the completed exudation; there is seldom craving for heated foods.

In the venesected cases the appetite returns but slowly; there is often a craving for hot food.

In the cases treated by venesection there is much greater wasting than in those treated by dietetic measures.

In the expectantly treated pneumonias the weakness vanishes with the completed exudation and the patient rapidly recovers; in the venesected cases the patient may feel better, but he has yet to go through a long siege of weakness.

The length of convalescence is much shorter in the expectant than in the venesectioning treatment.

Dietl realized that bleeding had but little effect upon the lesion. He says in this connection:

Clinical and physiological observations speak for the fact that bleeding has no power to limit the pneumonic exudate.

Venesection even favors the extension of the hepatization. Many in- and ex-tensive pneumonias occur and flourish under the lancet.

A few more generalized dicta remain; they lead us to a forceful climax.

A pneumonia left to itself is very seldom fatal.

Pneumonia treated by venesection is often fatal in itself.

The expectant treatment of pneumonia shows a much more favorable mortality record.

Venesection has a certain and none too innocent a part in the great mortality of pneumonia.

Venesection kills by increasing the blood disturbance.

Bleeding is not necessary to the re-establishing of health and therefore is not indicated.

Bleeding in many cases *works real harm*, and though no measure may at times give such striking and quick relief, yet the application of bleeding in pneumonia is to be limited to the utmost or, what is safer, is to be thrown completely aside.

## THE EARLY DIAGNOSIS OF PULMONARY TUBERCULOSIS.\*

By LOUIS HAMMAN, M. D.

On the afternoon of the twenty-first of February, 1905, a special meeting of the Laennec Society was held in this amphitheater to open with fitting exercises the Phipps Dispensary. The gifts of Mr. Henry Phipps had made possible the execution of the plan cherished for years by Dr. Osler to have a special department for the study of tuberculosis and the care of tuberculous patients. The old stable facing Monument street had been reconstructed into a two-story building to serve as dispensary and laboratory. On March 1 of the same year the clinic opened to receive patients. The meeting tonight, therefore, is the decennial commemoration of the opening of the Phipps Dispensary for Tuberculosis, and the occasion has for me a deep emotional content, since during these ten years I have been intimately concerned in its fortunes. The years have passed quickly, so quickly that I still feel somewhat the discouragement of the early struggle mingled with the enthusiasm of the period of highest activity and the satisfaction that the department has in the end earned a recognized place in the medical clinic of this hospital. The source of the greatest satisfaction to all of us who have worked in the dispensary is the belief that the attitude we have gradually come to assume towards the diagnosis of pulmonary tuberculosis has colored and perhaps even shaped the attitude that is now accepted by the medical clinic as a whole. It would be a pleasure for me reminiscently to unfold the gradual development of the dispensary; to dwell upon the men who have worked there so faithfully and of their influence upon the work, and to speak of the numerous publications that have come from the clinic and the laboratory. I wish I could describe to you the spirit of kindly and genial good fellowship that has pervaded the staff and has made the work so pleasant and personal contact among the members so delightful. However, dear as these memories

are to me, they have not the same force to move you and they deserve no place in a medical discussion. Nor does the time at my disposal allow me to review all of the medical work done in the dispensary. The opportunities offered us have directed our attention particularly towards the diagnosis of pulmonary tuberculosis. I have said that we have come to assume a certain attitude towards this problem, and, since we believe that this attitude sums up the best of our clinical work, I shall content myself with describing it and pointing out its bearing upon some general clinical and sociological questions. In describing the attitude I shall trace briefly the manner in which it has come gradually to be assumed, since I shall thus include justification with definition.

When the dispensary was opened interest in tuberculosis was already running at a high mark. During years of patient and persistent effort the medical profession had gathered small streams of enthusiasm into a large flood which had outrun the profession and was growing deeper and deeper with the inflow of wide-spread social interest. Tuberculosis could be stamped out—so the evidence seemed clearly to indicate—and since the way was there the means to follow it must depend only upon willing disposition and energy. I need not review the program of campaign other than to state that the diagnosis of pulmonary tuberculosis and its cure were essential features. Sanatorium reports gave glowing accounts of the prompt benefits of treatment, while at the same time insisting that these benefits were in direct proportion to the earliness of diagnosis. It was assumed that every case of pulmonary tuberculosis has an early stage; that this early stage can be diagnosed by the skillful; that early diagnosis insures recovery and, therefore, that the solution of the tuberculosis problem depends in large measure upon the diagnostic skill of the medical profession. "Tuberculosis is a preventable and curable disease" was the slogan, and the profession was preached to in and out of season about the necessity of early diagnosis and privately and pub-

\* Remarks made at the meeting of the Laennec Society, held February 24, 1915, on the occasion of the decennial of the Phipps Dispensary for Tuberculosis.



licly censured for its deplorable inaptness in this province of medicine. One was surrounded by the conviction that an enlightened profession could quickly save the day and stimulated to hope that by earnest appeal and vigorous pricking the conscience of the profession could be aroused to a sense of its gross deficiency and its heart warmed to yearn for the enlightenment that desire and honest effort would surely bring.

For the moment I shall not stop to separate truth from error in these statements. They are of interest now only to picture the atmosphere in which the dispensary work was begun. We were still young enough to feel the influence of enthusiasm at beginning a new work; to have an ear for the last word of authority; and loyal enough to our profession to feel the sting of opprobrium cast upon it and to resolve that at least in our small way we would by practice and influence contribute to make the rebuke unmerited. Our hearts were, as you see, in the right place regarding early diagnosis, but our skill was scarcely equal to what was demanded of it. This deficiency we sought to correct by assiduous application, and so earnest were our efforts that at the end of a year, or perhaps two years, we could pick out changes in the percussion note and slight alterations in the breath sounds with an agreeable nicety. At the end of that period we were making the diagnosis of pulmonary tuberculosis early enough to content the most exacting sanatorium physician—and that is saying a great deal. Indeed, I know no other way of expressing satisfactorily our interest, our enthusiasm and our finesse in physical diagnosis. In August, 1907, we published a short article on the early diagnosis of pulmonary tuberculosis which I have re-read with interest because it confirms the account I am giving you of our attitude at that early date.<sup>1</sup> The concluding paragraph of the article sums up the situation thus: "In conclusion we desire to express our opinion that in the diagnosis of an early case of pulmonary tuberculosis no abnormality of the physical signs should be disregarded, no matter how unimportant it may be at first sight. A single click, if it persists after coughing and deep breathing, and especially if it is heard at the same spot on subsequent examinations, should put us on our guard and arouse us to use all the means we have to make a correct diagnosis—whose importance is inestimable in these cases. Only in this way will it be possible to diminish the enormous mortality and morbidity which accompany this disease, and which are a disgrace to the medical profession which to-day, more than ever before, is responsible in large measure for the conditions of life resulting from tuberculosis."

This was the period of direct and simple satisfaction in the dispensary work. Slight abnormalities in the physical signs in any person with symptoms enough to bring them to the dispensary were regarded as evidence sufficient to justify a diagnosis of pulmonary tuberculosis and this diagnosis, followed by treatment in a sanatorium, or, in some instances, at home, gave just such gratifying results as were promised to reward enlightenment. However, even at that early day the seed of doubt had been sown and its growth was beginning to

trouble our faith in this simple and satisfactory plan. It is difficult to discover the source and observe the early growth of doubt; it generally obtrudes itself full-grown and unexpectedly upon our vision; however, I believe it was the use of tuberculin that first introduced it. In the report of 1907, already referred to, what we had done with the subcutaneous test and the conclusions we were willing to draw from its evidence are briefly considered. To my surprise I find there very clearly pointed out that a failure to react is very strong evidence against the patient having active tuberculosis; that a focal reaction is definite evidence of its presence; that a constitutional reaction is equivocal, since 60 per cent of healthy adults show such a reaction. I am particularly pleased to read the following: "It must be remembered that a patient may have a pulmonary disease other than tuberculosis and still react to tuberculin." "We are willing to admit that, relying upon its (tuberculin's) aid, we may send to the sanatorium some patients who would have recovered perfectly had they continued their accustomed mode of living."

In June, 1908, was published a complete report of our experience with the subcutaneous tuberculin test and a preliminary note upon the cutaneous and conjunctival tests which had been introduced the previous year.<sup>2</sup> During the first year of our work in the dispensary we began using the subcutaneous tuberculin test for diagnosis upon patients at Eudowood Sanatorium and St. Agnes' Hospital and subsequently upon ambulant patients. Of the first thirty patients tested at Eudowood all but one reacted, and we accepted these results as a satisfactory confirmation of our diagnostic criteria. However, a wider application of the test soon robbed us of this satisfaction, because it made apparent that, no matter how trivial the evidence of disease might be, tuberculin almost uniformly confirmed the slightest suspicion and indeed that many individuals with no valid evidence of tuberculous disease also reacted. About this time very enthusiastic reports of the value and importance of tuberculin diagnosis were coming from the German sanatoriums. A tuberculin reaction was given almost equal value in evidence as finding tubercle bacilli in the sputum and such statements as "The patients in this group all had tubercle bacilli in the sputum or else reacted to tuberculin" were frequently made as a guarantee that all the patients undoubtedly had pulmonary tuberculosis. Tuberculin was vaunted as the "sovereign means with which to establish the proper diagnosis with absolute certainty"; and "the quintessence of tuberculin diagnosis" was said to reside "in the Sicherstellung—the making absolutely sure of the diagnosis in doubtful cases."

We took at no time a part in this wave of tuberculin enthusiasm, which retains defenders to the present day. Our experience, together with the welcome statistics of Beck and Franz, ranged us strongly against it. A very conservative attitude is maintained throughout the report of 1908, an attitude the correctness of which subsequent experience has amply confirmed. Indeed, I have nothing of importance to add to what was then said about the subcutaneous tuberculin test and

<sup>1</sup>Hamman and Wolman: The Early Diagnosis of Pulmonary Tuberculosis. Johns Hopkins Hosp. Bull., 1907, XVIII, 299.

<sup>2</sup>Hamman: The Use and the Value of Tuberculin in the Diagnosis of Pulmonary Tuberculosis. Arch. Int. Med., 1908, I, 443.



nothing to retract, except perhaps a little overzealousness in the matter of detecting focal reactions in the lung. The diagnostic importance of a negative tuberculin test and of a focal reaction are duly emphasized and it is as clearly pointed out of what little value is a constitutional reaction alone in establishing a diagnosis of active tuberculous disease.

In May, 1909, and December, 1910, we published two extensive reports upon the cutaneous and conjunctival tuberculin tests<sup>3</sup> and the conclusions then reached are the basis for the interpretation we still place upon these tests. I know with what disfavor the conjunctival test is at present regarded and indeed, influenced by reports that reach me, I am willing to grant that the test should be neither generally nor indiscriminately used. However, I still believe that when proper care is exercised the test may be employed without fear. We have continued to use it in the Phipps Dispensary as a routine procedure and, while very rarely disagreeable reactions occur, I have observed no serious consequences to follow. We surely are beholden to the test for important clinical aid and I think our dispensary clinic would suffer a definite loss should subsequent experience necessitate its abandonment. As you know, we attach considerable value to the 1 per cent conjunctival reaction as confirmatory evidence of the presence of tuberculous disease and, though we have made the attempt repeatedly, we have been unable to draw an equally valuable indication from quantitative cutaneous tests. However, we have always insisted upon the same conservative interpretation of these local tuberculin tests that we have applied to the subcutaneous test, and we have consistently deplored attempts to stretch their meaning beyond the relative limits that critical study justifies.

From 1907 to 1910, the period during which our tuberculin studies were pursued with greatest diligence, a decided change gradually crept into our attitude towards the early diagnosis of pulmonary tuberculosis. There was attack and resistance in the clinic and contention among the staff before our present views were firmly established. As I have said, I think tuberculin was responsible for arousing the suspicion that matters were not so pleasantly simple as we had at first supposed, but suspicion, once aroused, led us quickly to review all the data upon which our conviction rested. This review drew our attention at once to the fact that only a small number of patients with signs of slight pulmonary disease could be sent to the sanatorium and that most of those forced to remain or voluntarily staying at home seemed somehow to be but little injured by the disease. True enough, the physical signs which were the main prop to the diagnosis did not disappear, but, on the other hand, neither did they advance and very few suffered the curse of onrushing disease which we were led to believe would surely follow indifference or neglect of these ominous forebodings. About this same time we were engaged in examining medical students and young women entering the hospital training school and, to our surprise, though they had

absolutely no symptoms of disease and were to all appearances in perfect health, still, in a large proportion, we found just such slight pulmonary abnormalities as those upon which, in the clinic, so much emphasis was being laid. Slowly values were readjusted and given what we now consider their true relation. At any rate diagnosis from then on came to mean something more than finesse in percussion and auscultation. At the same period, though of course to a less degree before, the clinic, or perhaps I should say the best men in the clinic, began to show an inquisitive interest in detecting non-tuberculous pulmonary disease masking as tuberculosis. An interesting group of non-tuberculous pulmonary infections was picked out; cases of spontaneous pneumothorax, unresolved pneumonia, empyema, pulmonary infarct, Graves' disease and others were recognized. I mention separately advance in the diagnosis of pulmonary conditions in children, a field in which diagnosis is so difficult, tuberculosis slipping in when least expected and lesions apparently tuberculous not rarely clearing up promptly.

Evidence of this readjustment soon appeared in our publications. In August, 1909,<sup>4</sup> reporting the results of tuberculin treatment among dispensary patients, we recognized the difficulties of early diagnosis and insisted upon establishing a separate group for those in whom the diagnosis could not be made with assurance, labeling this group "probable"; for the same reason a similar classification had been adopted in analysing the results of the conjunctival and cutaneous tuberculin tests. Again the relation of early diagnosis to sanatorium treatment is pertinently referred to in an article on the prevention of tuberculosis that appeared in February, 1910<sup>5</sup>—and the whole question is briefly considered in a discussion published in the Bulletin for July, 1911.

Up to 1910 we had used the Roentgen-rays in the diagnosis of pulmonary conditions only in special cases presenting unusual physical signs, or as a means of verification in doubtful cases. In the summer of this year Dr. Dunham, with the assistance of Dr. Boardman and Dr. Wolman, undertook to study the value of Roentgen-ray examinations in the diagnosis of pulmonary tuberculosis. A special apparatus was installed to facilitate this study and for four months the work was devotedly pursued. A report of the investigation was published in July, 1911.<sup>6</sup> Bearing upon the question of early diagnosis the study revealed an unexpectedly close agreement between the results of physical and Roentgen-ray examinations. It is true that the roentgenograms showed more extended lesions than would have been anticipated from the physical signs, but the location and, to a less degree, the extent of the changes were for the most part accurately predicted before the pictures were taken. This work, taken in conjunction with many other similar studies, demonstrates with what wonderful pre-

<sup>3</sup>Hamman and Wolman: Tuberculin Treatment Among Dispensary Patients. Johns Hopkins Hosp. Bull., 1909, XX, 225.

<sup>5</sup>Hamman: The Prevention of Tuberculosis. Jour. Outdoor Life, 1910, VII, 29.

<sup>6</sup>Dunham, Boardman and Wolman: The Stereoscopic X-ray Examination of the Chest. Johns Hopkins Hosp. Bull., 1911, XXII, 229.

<sup>3</sup>Hamman and Wolman: The Cutaneous and Conjunctival Tuberculin Tests in the Diagnosis of Pulmonary Tuberculosis. Arch. Int. Med., 1909, III, 307; *ibid.*, 1910, VI, 690.



cision changes of density in the lung may be outlined by the Roentgen-ray. Unfortunately, however, Roentgen-ray examinations applied to the early diagnosis of pulmonary tuberculosis suffer all the shortcomings inherent in physical examinations; indeed, they have these short-comings to a still greater degree. Briefly, their inadequacy depends upon this, namely, that, though they give us a precise picture of pulmonary density, nevertheless from this picture we cannot draw either etiological or physiological conclusions. Thus, as regards tuberculosis they do not distinguish active from inactive lesions, which is the important clinical decision. Physical examinations are subject to the same criticism, but they have a decided advantage over Roentgen-ray examinations, in that they discover not only density but moisture as well.

At this time, that is, in 1911, conservatism was the note of the dispensary attitude towards the early diagnosis of pulmonary tuberculosis, and a diagnosis based upon insufficient evidence, especially when slight changes in the physical signs afforded the only evidence, was no longer tolerated. We were gradually getting upon our records valuable data which would in due time decide the practical outcome of the more rigid standards we had set. A study of these records was begun in 1912.<sup>7</sup> For this study a thousand cases were selected, which had some years before been carefully tabulated for the second report upon the conjunctival and cutaneous tests. The later history of these patients was sought by personal interview and letter and satisfactory data concerning 632 were obtained. In the present connection we are interested only in the doubtful group of cases comprising 258 of the patients. Had the analysis shown that a large number of doubtful cases had subsequently become tuberculous, then our conservatism would have been condemned and banished. However, far from showing anything of that sort, the analysis has furnished the very strongest support to our conservatism. Of the 258 patients reported upon, 176 were well; 57 unimproved, that is, the symptoms that had brought them to the dispensary still persisted; 16 had become frankly tuberculous; 9 had died of some cause other than tuberculosis. I must refer you to the report for a closer study of the interesting figures, for, although 6 per cent of the patients became tuberculous, a relatively large number, still the character of these 16 cases will give you a better notion of how much emphasis the figure merits.

There is only one more study to mention and the notice will be brief.<sup>8</sup> I have said that in making routine physical examinations of a large number of students and nurses our attention was early drawn to the frequent occurrence of more or less marked apical abnormalities in perfectly healthy adults. To put this experience in precise form, we studied with unusual care the pulmonary physical signs in fifty healthy students and controlled the physical findings with roentgenograms. As

we anticipated, a large number showed definite abnormalities on physical examination, abnormalities that were confirmed by the Roentgen-ray findings. The roentgenograms are particularly instructive in calling attention to the extensive changes present in the lungs of healthy adults about whom hovers no suspicion of active pulmonary disease. There are some who now consider the Roentgen-ray "the sovereign means with which to establish the proper diagnosis with absolute certainty" in early pulmonary tuberculosis, just as others hold tuberculin to be this regal means. I believe studies similar to the one we have made will have a sobering influence upon their enthusiasm.

You must see now to just what point our ten years' study of the early diagnosis of pulmonary tuberculosis has brought us. Not the anamnesis, nor the physical examination, nor tuberculin, nor the Roentgen-ray, nor any other means with which we are familiar, taken alone, is adequate in the making of a decision in this momentous question. Diagnosis here, as in nearly all other fields of internal medicine, is reached through skill, judgment, and experience; skill in the application of methods; judgment to carefully weigh the results, and experience to give them the proper interpretation. While exploration of the lungs is, in my opinion, the most difficult domain of physical diagnosis, still I would insist that the early diagnosis of pulmonary tuberculosis rest upon many pillars and not be supported alone by finesse in percussion and auscultation.

Throughout these remarks I have spoken of "slight abnormalities in the pulmonary physical signs" and have been rather severe in my criticism of what I consider the undue importance that has been attached to them in early diagnosis. It remains for me to make perfectly clear, if I am able to do so, just what is meant by "slight abnormalities." In relation to physical diagnosis, the medical profession may be divided into the skillful and the unskillful. I am forced to say, from my own experience, that the vastly larger number is unskillful. I hasten to add that the judgment is passed in no spirit of criticism or censure, for proficiency in the arts of pulmonary auscultation and percussion is reached and maintained only by close and persistent application; an attention which most practitioners have neither the time to give nor sufficient motive to cultivate. To the group of physicians to whom even relatively gross lesions are a source of difficulty and uncertainty in diagnosis, I have at present nothing to say. I have elsewhere expressed the opinion that much more will be accomplished by encouraging them to observe closely and critically the general symptoms of the disease than by insisting upon skillful examinations. It should be urged particularly that when obvious symptoms are present their importance be not subverted by a so-called negative examination.

The physicians skillful in physical diagnosis may be subdivided into those more and those less skillful; the more skillful being represented in the main by sanatorium physicians and those particularly interested in tuberculosis, the less skillful by those engaged in the general field of internal medicine who, nevertheless, on account of the prominent position occupied by

<sup>7</sup> Gelien and Hamman: The Subsequent History of One Thousand Patients Who Received Tuberculin Tests. Johns Hopkins Hosp. Bull., 1913, XXIV, 180.

<sup>8</sup> Hamman and Baetjer: Pulmonary Physical Signs and Roentgen-ray Findings in Healthy Adults. Arch. Int. Med., 1914, XIV, 757.



pulmonary disease in this field, are made daily to practise and display their skill in percussion and auscultation. The former group, on account of specialized training, has the greater skill, but I believe it has allowed virtuosity somewhat to obscure its judgment; the latter group, on account of wide experience, has the better judgment, but I believe it has allowed wide interest somewhat to dull the practice of its art. Both groups, however, will appreciate the bearing of my remarks and sympathize with my difficulties.

To return now to the definition of slight abnormalities in the pulmonary physical signs. By these I mean slight differences between the two sides of the chest on inspection; slight changes in the percussion note, situated practically always at the apices; slight changes in the intensity and quality of the breath and voice sounds, also nearly always at the apices. Any obscurity in this definition resides in the word "slight" and it was in preparation for this difficulty that I arbitrarily grouped the profession into the skillful and the unskillful as regards physical diagnosis. Had I the gift, which I have not, of the most penetrating lucidity of expression, I could not clear away this difficulty for the unskillful, whereas the skillful will appreciate its meaning without further ado. In comparing the value of physical signs with Roentgen-ray findings in pulmonary diagnosis I have already said that the former has an immeasurable advantage, in that it detects moisture as well as difference of density, and I will conclude my remarks on this aspect of the subject with a few words about the significance of râles. Let me add that by râles I mean the definite moist sounds that are heard at the apices at the end of inspiration and commonly enough only after cough; and that I do not mean the various transient clicks and so-called adventitious sounds that may simulate râles so closely and often puzzle the adept and mislead the novice. Allow me further to qualify what I am about to say by adding that I refer to localized râles found when all the other clinical features of the case in question make a diagnosis of pulmonary tuberculosis not only reasonable but probable. For instance, râles, even at an apex, would have quite a different significance if the symptoms and other physical findings pointed frankly to the diagnosis of lobar pneumonia. These restrictions being clearly understood, I am prepared to state upon wide experience that when localized râles are discovered in the presence of symptoms and other physical signs pointing towards pulmonary tuberculosis, the diagnosis is practically assured; and by diagnosis I mean a clinical, not an anatomical, diagnosis; or, in other words, that the patient has an active tuberculous lesion. The discovery of râles, thus restricted, I place second only to the finding of tubercle bacilli in the sputum in the diagnosis of pulmonary tuberculosis. Alas! when we possess the assurance that râles give us, for the sanatorium physician the patient has already passed out of the class favorable for treatment.

In concluding, I return to the tenets that comprised our faith at the opening of the dispensary to see how these have fared in the light of more mature experience. You will remember that we were guided by the belief that every case of pulmonary tuberculosis has an early stage, that this early stage can be

diagnosed by the skillful, that early diagnosis insures recovery and, therefore, that the solution of the tuberculosis problem resides to a large measure in the diagnostic skill of the medical profession. How have we departed from the simple faith of our childhood and how scepticism and dissent have corroded this creed! The very first premise—that every case of pulmonary tuberculosis has an early stage—is tinged with gross error. Tuberculosis is not an infection that always begins as a minute lesion in the lung, from which lesion the disease gradually and slowly spreads to neighboring areas, giving at first but indefinite signs of its presence and only later causing obvious symptoms. Rather, it commonly strikes abruptly and unexpectedly; it pounces upon an individual in full health and then continues, as it began, not with slow progression, but by leaps and bounds. A large number of cases of pulmonary tuberculosis have no early stage, but jump at once from health to a moderately advanced or advanced stage of the disease. Thus a man starts out in the morning upon his affairs in his usual good health; in the afternoon he feels draggy and feverish; he keeps to his bed, runs a fever and begins to cough; little is found immediately upon examination, but two weeks later half a lobe or a whole lobe is involved; another has hemoptysis, followed by a similar course of events; still another begins with "grip" and though not ill enough to remain in bed still can name the very day upon which the illness began. I repeat, clinically the disease as commonly begins in some such abrupt manner as in the slow, creeping fashion that propagandists delight to picture. Were it not so, then why is it that early cases of pulmonary tuberculosis so persistently elude us? We see very few cases of incipient tuberculosis in the dispensary and we have a large and varied material to draw from, an unusually favorable material from which to pick out early cases. If you say that our standards of diagnosis are too rigid, then I point to our results for justification; if you say that patients do not present themselves for examination early enough, then I reply that we have examined large numbers of exposed individuals and have failed to find early tuberculosis. If it were possible to have all the inhabitants of Baltimore submitted to ever so rigid a clinical investigation, I firmly believe that it would be impossible to pick out those who will be frankly tuberculous at the end of a month. Once having taken our present stand on the early diagnosis of pulmonary tuberculosis, few cases that are definitely tuberculous will fall into the incipient group. The reason for this I believe resides more in the nature of the disease than in lack of diagnostic ability.

The second premise—that the early stage can be diagnosed by the skillful—I need mention only briefly. What has just been said robs it at once of half its importance. Concerning the other half I would remark that the necessary skill will never be the common possession of the profession as a whole. We have no more right to demand of it exceptional training in this field than in any other special field of medicine and to master them all is quite impossible.

That early diagnosis insures recovery is in a measure true and if we change "insures recovery" to "makes recovery likely" we are still nearer the truth. What I have said of the difficul-



ties of early diagnosis offers an explanation for the very small number of cases of incipient tuberculosis that we find in sanatoriums. I say in sanatoriums, because it is there that we would naturally expect to find them and because it is there that we look also for a demonstration of the effectiveness of treatment. In sanatoriums there are two classes of cases: the definitely tuberculous and the questionably tuberculous. How many of the former, how many of the latter, will depend somewhat upon the questioner. As definitely tuberculous we may include those with tubercle bacilli in the sputum and those with frank signs of pulmonary involvement, meaning by frank signs impairment of the percussion note, change in the breath sounds and moist râles. Although a few of the patients showing such frank signs will upon careful investigation prove to have non-tuberculous pulmonary affections, this number will be too small to introduce a serious error. In this definitely tuberculous group the results of treatment depend largely upon intelligent co-operation and the financial possibility to co-operate. Thus among the intelligent with a reasonable income the results will be good, whereas among the poor the results will be most discouraging. Unfortunately, tuberculosis is prevalent chiefly among the poor and the results obtained at state sanatoriums with this class of definitely tuberculous patients have been very disappointing. Temporary improvement is usually followed by prompt relapse when the patients return home to their unsatisfactory living conditions. The questionably tuberculous group includes those patients without the specific clinical marks of tuberculous disease. Many of them have symptoms strongly suggestive of the disease without definite physical signs; others have both indefinite symptoms and signs. While there can be little doubt about the diagnosis in some of these patients, still in a large number the diagnosis rests in a measure upon individual opinion, a very hazardous prop for cogent conclusions. It is in this group that treatment brings about such brilliant results, results which without warrant have been transferred to the treatment of pulmonary tuberculosis as a whole and have led to exaggerated notions of the curability of the disease.

Having taken exception to all the premises, it is needless to add that we no longer have faith in the conclusion that the solution of the tuberculosis problem resides to a large measure in the diagnostic skill of the medical profession. Were it possible—though we think it is not—to train the profession to a high standard of diagnostic skill, still the nature of the infection and the difficulties encountered in early diagnosis, even by the expert, would be an insuperable barrier to such skill becoming an effective weapon in the campaign against tuberculosis.

To those of us who have worked in the dispensary since its first years this gradual change in attitude towards early diagnosis has been a stimulating source of interest. The change has come unsought, indeed in a way unwelcomed, for it has shattered agreeable delusions and robbed us of fond hopes. We would have been better pleased had our early impressions been confirmed, and as the evidence we slowly amassed pulled us from our first position, we followed unwillingly the path to

which it led. The point at which we have arrived is not the satisfactory resting-place we expected to find when we began the journey. Nor do the prospects that confront us justify the cheer of anticipating a speedy deliverance from our difficulties. However, we still have faith and we hope that in the end some way will be found to separate from the large group of doubtful cases that smaller group in whom mild symptoms and slight abnormalities in the physical signs presage the onset of more serious clinical manifestations. If we can ever distinguish clinically that nice point where latent infection first passes into threatening activity, the problem of early diagnosis will be solved. At the present time this point is blankly obscure and we have no means of deciding definitely which doubtful cases are within safety, which have just passed without, and which are hovering about the threshold. Hence it results that early diagnosis is so largely a matter of personal judgment, that it has no fast and sure rules to guide it and that at present there is such a wide difference of opinion within the profession as to what shall be included in the group of early pulmonary tuberculosis. I hope I have made clear to just what attitude towards this important question ten years of sincere and earnest work has brought the Phipps Dispensary.

#### DISCUSSION.

DR. HURD: I should like to make an inquiry. What would Dr. Hamman advise us to do for these cases? If it is impossible to find out what is the matter with them, what is the practical application? Shall we keep up our sanatoria and dispensaries, or shall we let them all go? Have we made any progress?

DR. JANEWAY: Perhaps I may be pardoned for saying a few words about Dr. Hamman's paper, as it gives perhaps the only aspect of this subject about which I know enough to have any reasonable right to an opinion. I have been in the position for a number of years of having to arrive at these judgments of which Dr. Hamman speaks and I am in complete accord with his point of view. We are at present face to face with hard facts, and though perhaps the whole blame for the failure to solve the problem of tuberculosis in a short time is not to be borne by the medical profession, nevertheless, it is clear that the lead must come from the medical profession and it is incumbent on us to face the facts and to make a fresh start.

It seems to me that the discussion of the early diagnosis of tuberculosis is more or less academic, with our knowledge of the dissemination of tuberculosis throughout the community and the early age at which infection in a large proportion of the cases takes place. We have to distinguish at once, of course, between the diagnosis of tuberculous infection and the diagnosis of tuberculous disease; but I am inclined to think we have to go further and that what we can aim at practically is perhaps a diagnosis for purposes of prognosis and treatment rather than absolute diagnosis in itself. In order to arrive at that, we must take into consideration other features of the case than those which bear only on diagnosis—in particular such matters as family history and the well-known age and sex factors which enter into the prognosis of the disease; because after all we are aiming at a diagnosis which will determine our advice to the patient. Shall we or shall we not send such a patient to a sanatorium? Shall we, with a patient known to have early and perhaps slightly active tuberculous disease, risk a period of observation at home in order not to inflict a serious economic or personal hardship upon the patient. Those are the difficult ques-



tions which come to us to be solved, and the mere making of the diagnosis does not solve them. We have to individualize absolutely. It is quite clear to me that while physical diagnosis has, as Dr. Hamman pointed out, very striking limitations, and while it is clearly incumbent upon the student above all things to learn the limitations of the methods with which he works, on the other hand, for the bulk of you who are here this evening, the acquisition of such extraordinary acuteness in diagnosis that you find much in the chest that is not there, is not a particular danger. For the next ten years of your lives, practice in the refinement of physical diagnosis will not work much harm to your patients. At the end of that time, you will undoubtedly come to the conclusions Dr. Hamman has reached.

There are a few factors which enter into the early diagnosis of tuberculous disease, however, on which it is desirable to lay emphasis. One of those, in my opinion, is the significance of hæmoptysis. I have seen, in the course of my experience, so many patients who were told that a little hæmoptysis was a bleeding from the throat and of no significance, that it has made a very strong impression. There is no symptom of tuberculosis which helps more in securing the co-operation of the patient in measures which you recommend than hæmoptysis. A patient who has once seen blood will do almost anything you tell him, if you catch him early. My experience, and the experience of my father before me, which was very definite in that regard, has been that patients with hæmoptysis have on the average a better prognosis than almost any others, partly because of the co-operation which you get from them.

The other feature, I think, is the existence of localized fine râles. Though, of course, râles are not an early physical sign, they are sometimes the earliest decided physical signs detected. I have seen patients in whom râles, in spite of repeated examinations, were really the only physical signs I could be sure of, go ahead to complete recovery, although they had bacilli over considerable periods. I remember one instance of this in New York City; a man who continued to pursue his occupation of traveling locksmith and who was perfectly well ten years afterwards, although I had found tubercle bacilli for six months and râles at the apex.

The question of diagnosis must be approached from another standpoint also. One must bear in mind not only what combination of symptoms and signs is highly suspicious of active tuberculosis, but in addition the other possible diseased conditions which may produce the same combination of symptoms and signs. For a number of years I have had to go occasionally in consultation to the Loomis Sanatorium, where I was a member of the medical board, practically always to solve diagnostic problems in regard to some patient sent in for pulmonary tuberculosis, who, after remaining there for from three to six months, could not be proved to have had it. The condition which most frequently caused these errors in diagnosis was perhaps first of all chronic infective endocarditis (*streptococcus viridans*). I have seen a number of patients who, because of the existence in the lung of evidence of focal broncho-pneumonia with low fever and loss of strength, were said to have pulmonary tuberculosis, the significance of the occasional eruption of petechial spots having been overlooked. Then again there is Hodgkin's disease, with relapsing fever. The differential diagnosis is extraordinarily difficult at times. Or, certain cases of hypernephroma with lung metastases, and a few of the rare primary tumors of the lung, where the distressing cough and loss of flesh, with lung signs lead to the diagnosis of tuberculosis. Lastly comes tertiary syphilis with fever. Then, of course, there is one standing reproach, which comes up in every hospital and tuberculosis dispensary—the appearance of the patient with an old mitral stenosis with recurrent hæmoptyses and recurring attacks of bronchitis, who is sent off to die of tuberculosis. These patients are rarely supposed to be early cases.

I think you ought to bear the above conditions in mind and in approaching any diagnostic problem do so from the two sides: First, the positive evidences of the condition one must suspect; and second, what other conditions might account for the existing symptoms. Then, arrive at a diagnosis by exclusion.

The importance of all this is because the treatment of this disease involves very serious economic and personal hardships and one ought not to require of any patient who can just make his living and keep his head above water, a long standing residence in a sanatorium if he has not the disease for which the sanatorium does good. In dealing with the well-to-do, the attitude of mind can be the opposite, and one can very wisely tell the patient, or the family, that while positive diagnosis is impossible, the present is the favorable time to act.

One other thing to be emphasized is the significance of a previous pleurisy with effusion. Where that is known to have occurred, one ought usually to assume the probable existence of pulmonary tuberculosis on the development of subsequent symptoms and signs.

DR. HAMMAN: In approaching such a large subject as the "Early Diagnosis of Pulmonary Tuberculosis" it is necessary to view the field from a single standpoint. I wish to call attention particularly to the fact that my remarks concerned the early diagnosis of pulmonary tuberculosis only from a broad, sociological standpoint, and not from the standpoint of early diagnosis as concerns the individual patient. In regard to the latter standpoint, I can add little to what Dr. Janeway has said. I am sure that no one could be more eager to make an early diagnosis than I am and I realize fully that the mistakes of the profession are more on the side of hesitating to make a diagnosis, when the conditions fully warrant it, than in making a diagnosis prematurely. As concerns the individual, treatment, which is the ultimate object of diagnosis, depends upon many factors other than strictly medical data. The position of the patient, the amount of leisure at his disposal, his financial condition and business obligations must all be taken into consideration. I have no quarrel with the physicians who treat doubtful cases of pulmonary tuberculosis. Indeed, in many instances I think such treatment is desirable. What I do quarrel with is the tendency which obtains in some quarters to treat these cases as definite instances of pulmonary tuberculosis and to add them to the list of sanatorium cures.

In reply to Dr. Hurd, I would say that to my mind all of the work that has been done has by no means been wasted. I regret very much that my remarks have left the impression that I look upon the situation in a pessimistic way. I believe, indeed, that a great deal of good has been accomplished, but I am thoroughly convinced that the early diagnosis of pulmonary tuberculosis will not play an important part in eradicating tuberculosis as a disease of the masses.

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# RESULTS OBTAINED FROM THE INDUCED PNEUMOTHORAX TREATMENT OF PULMONARY TUBERCULOSIS: A BRIEF REPORT.\*

By MARTIN F. SLOAN, M. D.

Three years ago Hamman and Sloan presented before this society a report covering a series of 20 cases of chronic pulmonary disease treated by the induced pneumothorax method. To-night they wish to add 23 cases to their series and present in a brief way the results that have been obtained.

It probably seems strange that, with such a large number as have been seen at the Phipps Dispensary to select from, comparatively few patients have been given the benefit of this treatment, but with a clearer understanding of the pertinent points of the procedure the explanation becomes apparent. The whole subject may be discussed conveniently under the four following headings: selection of patients; technique of the inflation; subsequent inflations; duration of collapse.

*Selection of cases.*—Three years ago the observation was made that, while induced pneumothorax would be of inestimable benefit to a number of cases, it would never become a routine treatment of chronic pulmonary disease, especially tuberculosis. This observation is confirmed by the broadened experience of three years and a judgment matured by a larger number of patients subjected to the treatment. The author selects as suitable for the method patients showing:

(a) Gross and active lesions in one lung, with a quiescent lesion not extending below the level of the fourth rib in the other lung;

(b) Gross and active lesions in one lung, with a mildly active lesion not extending below the level of the third rib in the other;

(c) Quiescent lesions, bilateral but suitably located, with a history of aggravating cough and profuse expectoration;

(d) Arrested lesions, but with a history of recurring hemorrhages;

(e) Arrested, but suitably located lesions, with a previous history of relapse whenever work was attempted.

Patients with incipient lesions have been considered unsuitable, except in cases of hemorrhage, as it was felt that the general natural therapeutic measures should be thoroughly tried before recourse to a radical treatment was made. All the patients treated had moderately or far advanced pulmonary tuberculosis, except one, who had bronchiectasis.

Those designated as unsuitable were patients showing:

(a) Gross and active lesions extending below the level of the third rib on both sides;

(b) An extensive gross lesion in one lung and a lesion located at the base in the other;

(c) Serious complications, such as cardiac disease, arteriosclerosis, ulcerative laryngitis, chronic diarrhoea, extensive tuberculous ostitis and nephritis, either acute or chronic;

\* Read before the Laennec Society, February 24, 1915, on the occasion of the decennial of the Phipps Dispensary for Tuberculosis.

(d) Disease apparently of long standing, as shown by marked fibrosis of the lungs, thoracic deformities, decided cardiac displacement and dyspnea;

(e) A history of chronic alcoholism;

(f) A history of recurring hemorrhage from both lungs;

(g) A marked emphysema;

(h) An erratic and excitable temperament;

(i) Real or apparent old age.

*Technique.*—The technique was that developed by Professor Forlanini, of Pavia. Three patients of this series were first subjected to the Brauer method, but the results did not justify the continuation of such a painful and prolonged technique. As a matter of convenience to the operator and comfort to the patient the Forlanini method has proved to be the more practical. A full description of this technique may be found in the BULLETIN of February, 1913, to which the reader is referred.

*Subsequent inflations.*—Compression of the lung was induced slowly, giving the other lung and the heart time to readjust themselves. For the initial inflation 500 cc. of gas is sufficient. No absolute rule can be laid down governing the amount to be given or the length of intermissions between subsequent inflations. One is guided by the terminal pressures of the preceding inflation, the estimated amount of gas absorbed since the last inflation, the pulse rate and temperature curve, the effect on weight, cough and expectoration, the patient's general feeling, and particularly by the condition of the working lung. The patients of this series have received, as a rule, 700 cc. of gas at the first inflation, which was followed by a like amount every three days until three inflations had been given. Every two to three weeks thereafter from 500 to 800 cc. were injected. Experience has shown that the smaller amounts of gas frequently administered produce better results than the larger amounts given at longer intervals. When the object of the treatment is to check pulmonary hemorrhage, it is desirable to exert pressure against the bleeding points as quickly as possible, and in such cases as much as 1000 cc. has been given during the initial inflation. The presence of pleural adhesions will upset any previous thought-out plans.

*Duration of collapse.*—It is exceedingly doubtful if healing sufficient to withstand the resumed functional activity of the treated lung can occur in a shorter time than two years. In Case III of this series the lung, which had been completely collapsed for a year, was permitted to re-expand at the end of that time. Four months after expansion had become complete and functional activity had been resumed, signs and symptoms of activity re-appeared. Nine attempts were made in different places, but nowhere was it found possible to introduce the gas. The pleural surfaces had adhered apparently throughout the entire side. This same experience



was encountered subsequently in two other cases. In the absence of contra-indicating symptoms, such as shortness of breath and persistent loss of weight, there is no reason why compression should not be continued indefinitely, if the working lung is holding up well and the patient is not uncomfortable or inconvenienced.

Briefly, the results in this series of 43 patients treated are grouped as follows:

*Special indications for relief.*—Case III was having repeated small hemoptyses. There was no recurrence as long as compression was maintained, which was for 16 months.

Case V had a pleural effusion. The effusion was removed and nitrogen introduced.

Case IX had had several frank hemorrhages and was having repeated hemoptyses at the time of the first inflation. Before compression became complete she had several more. She has had none since March, 1912.

Case XI gave a history of frank hemorrhages to within two weeks of the initial inflation; there was no recurrence to the time of death 26 months later.

Case XII was developing a cavity in the upper lobe of the right lung and was having small hemoptyses therefrom. There was no recurrence after compression.

Case XIII gave a history of several large hemorrhages with repeated small hemoptyses up to the time of the first inflation; there has been no recurrence to date, three years and three months after.

Case XVI was having profuse hemorrhages at the time of the first inflation; there was a small hemoptysis 12 hours later. There was no recurrence until eight months later, when hemorrhage started again from the treated lung in spite of an almost complete collapse.

Case XIX was having repeated hemoptyses prior to and at the time of the first inflation. There has been no repetition to date, two and a half years later.

Case XX gave a history of repeated hemoptyses. There was relief for over a year, after which bleeding started from the "opposite" lung.

Case XXI, one of bronchiectasis, gave a history of repeated hemorrhages from the right lung. There was relief for three months following the first inflation, after which bleeding started from the left lung.

Case XXII gave a history of repeated attacks of pleurisy on the right side with sharp pain. The pain was relieved for over a year by partial collapse of the lung.

Case XXX gave a history of repeated hemoptyses. There had been no repetition after 20 months' treatment.

Case XXXII gave a history of profuse hemorrhage prior to the first inflation. There had been no repetition after 18 months of treatment.

Case XXXIII was developing a cavity in the upper lobe of the right lung. There has been perfect health for the past year.

Case XLIII gave a history of repeated hemoptyses. There has been no recurrence since the first inflation over three months ago.

Cases not specified in this group were treated for progression of the disease.

*Accidents and Early Death.*—Case I developed a pleural effusion which, more than a year after the inflations had been discontinued, became purulent. The pleural cavity was drained through an intercostal space. The wound healed and the patient has been doing splendidly for the past two years.

Case X developed meningitis after the third injection and died 14 days later.

Case XVIII was in a desperate condition when treatment was started and died ten days after the first inflation.

Cases XI, XII, XIII and XXXIII developed a hydrothorax. The fluid became purulent in Case XI a year and a half after the last inflation and the patient died two months later. In Case XII, pyothorax developed three months after the last inflation, from which the patient subsequently died. Cases XIII and XXXIII have been enjoying perfect health for three years and for nine months, respectively, after the development of fluid. A slight amount of fluid persists in each case.

Case V had extensive pulmonary tuberculosis and a pleural effusion. The effusion was partly removed and sterile air injected. The fluid became purulent after the third inflation. Resection and drainage were instituted, but the patient died three and a half months later.

*No collapse produced.*—Adhesions were so extensive and dense in five cases that it was impossible to inject the smallest amount of gas. The Brauer method was tried in Case VI without satisfactory results. Punctures were made in all available areas of the hemothorax without finding a patent pleural space.

*Partial collapse produced.*—Owing to adhesions only a partial collapse was produced in 15 cases. The partial collapse existed in various places, the base being held firmly to the chest wall as frequently as the apex. Those in whom only a partial collapse was produced seemed to experience as much symptomatic relief as those in whom a complete collapse was obtained.

*Complete collapse produced.*—A free pleural space was found and a complete collapse obtained in 17 cases. In several of these it was found advisable to maintain only a partial collapse in the course of treatment owing to a flexible mediastinum, permitting encroachment on the working lung, and to a cardiac displacement.

Of 43 patients treated from three months to three and a half years 18, or 41+ per cent, have died, and 25, or 58+ per cent, are living. Of these 25 living, 8, or 19+ per cent of the whole, are doing poorly; 11, or 26+ per cent, are doing well and are working part time. Some of these are inclined to resume their former full working time, but refrain from doing so on medical advice. Six, or 14+ per cent, have resumed all of their former business and social obligations. Five of these have been working for over two and one-half years.

The induced pneumothorax treatment applied to the 42 patients with moderately or far advanced pulmonary tuberculosis and one with bronchiectasis, and in whom the prognosis was bad, influenced the progressing course of the disease little or none at all in 60 per cent. That it did, however, stop dis-



tressing symptoms in a large number of these is shown by a careful inspection of the individual charts. That it has given to 11 per cent perfect health and complete working capacity for over two and one-half years certainly justifies the use of the method and establishes it as a valuable addition to our therapeutic armamentarium.

#### DISCUSSION.

DR. WOLMAN: Sometimes in desperation people rush in, perhaps foolishly, where angels would fear to go. I say this in connection with the cautions Dr. Sloan has laid down in administering pneumothorax. He insisted that the better lung ought to be perfectly good. I can recall two cases which have led me to be a little more optimistic than those pessimists associated with me. One sometimes has the feeling in the presence of a dying person that it might be well to undertake even measures that everyone has said will do no good. We happened to have a girl at Reisters-town who attracted everyone by the sunniness of her disposition. She was very sick with a high fever, rest in bed for a long time having had no effect upon her symptoms. We had thought of pneumothorax, but decided it was contra-indicated, because it was hard to tell which was the better lung. However, in desperation we thought we might try it. The result was most beneficial, the fever dropping almost spontaneously. Of course the girl may not be cured, but she has every chance of gaining a few years of comfortable life. It is said that another contra-indication is tuberculous laryngitis. Unfortunately, this girl had that, too. However, the laryngeal lesion improved also. I do not say this to cast doubt on Dr. Sloan's injunctions, but simply because it seems to me that there are some cases in which it can do no harm to try the treatment and in which the patient may receive much benefit.

The second case was that of a man with a bilateral lesion, who had been in bed for about a year, with fever, and who had diabetes also. We were afraid to try pneumothorax on account of the diabetes, so we sent him to the Sanatorium. Dr. Cullen sent him back, however, in a few weeks, saying he ought to die with his family. In this case nature attempted what mortals were afraid to do, and he evolved a spontaneous pneumothorax. The man almost died, but after the first week he improved and the fever which had been running for a year disappeared. These cases would seem to show that some cases with apparent contra-indications will perhaps be benefited by this form of treatment.

DR. HAMMAN: I should like to emphasize just one point in regard to the patients Dr. Sloan has exhibited, namely, the advanced stage in which the disease existed in these patients when treatment was begun. I remember particularly the robust young man who was seated in the center. He was quite ill when the treatment was begun, nearly three years ago. He had had a

number of severe hemorrhages and had at the time considerable fever and was markedly prostrated. We were just beginning to induce pneumothorax at that time and I think he was given too much air at the first few operations. He failed to improve satisfactorily until he developed an abundant effusion on the right side. Following the development of this effusion he improved in a remarkable way and during the past year has worked actively as an insurance solicitor and has remained in very good condition as you could easily see. The effusion has persisted and his right lung remains completely collapsed. In about one-third of the cases in which we have succeeded in inducing pneumothorax such similar effusions have developed and in these patients it is practically certain that the functional capacity of the lung will be permanently lost. This tendency towards the development of massive effusion makes the treatment undesirable in the early stages of pulmonary tuberculosis. Since, roughly speaking, one-third of these cases will permanently lose the function of the lung, it would be inadvisable to use the treatment until the effects of the ordinary hygienic and dietetic measures had been thoroughly tried out. Of course it is equally important not to delay the treatment too long and if under favorable conditions such early or moderately advanced cases fail to improve, if the conditions are otherwise favorable, pneumothorax should be employed.

DR. SLOAN: I feel in beginning a new and radical treatment like this one we should do so in a conservative manner. Up to the present time we have been more or less conservative in selecting our candidates; in fact, during the last two years we have inclined more and more to conservatism. Dr. Wolman is evidently going through the same period we went through in our early experiences with the process. I believe in the future the tendency will be to select earlier cases for treatment when, especially after observation, it is seen that under the ordinary treatment the patients are likely to do badly.

I think we are entirely justified in selecting the early cases whose histories show a breakdown on any attempt to resume their occupations.

In regard to what Dr. Hamman says about effusions, it is true that a good many of the patients develop an effusion, but in our last 12 patients with complete collapse we have not had a single one. It is difficult to account for the development of this complication. We thought at first it was due to obstruction of the circulation in the pulmonary lymphatics, but in some cases the effusion did not develop until the most favorable condition for this complication—the period of complete collapse—had passed and the lung had almost re-expanded and resumed its function. Neither does it seem to be due to trauma, such as occurs when adhesions are stretched; yet it does appear occasionally at this time.

## A BRIEF EPITOME OF THE RESULTS OF SANATORIUM TREATMENT.\*

By S. WOLMAN and I. I. HIRSCHMAN.

It is natural that the sanatorium should view with greater optimism the results of sanatorium treatment than the dispensary, which sees the discharged patients after they have returned to their homes in the city and have attempted to re-enter the economic life.

Our general impression, built upon what we saw in the daily routine of the Phipps Dispensary, was that the results of treat-

ment were frequently disappointing. In order to test the validity of our impressions, we studied the list of admissions to the State Sanatorium since its opening, and without any selection whatever identified as many as possible of those patients that had been examined at the Phipps Dispensary. We included also in this study a comparatively small number of patients who had been at local sanatoria other than the State Sanatorium.

We examined the histories of 403 patients who had had the advantages of sanatorium treatment. Of these, 262 had to be

\* Remarks before the Laennec Society, February 24, 1915, on the occasion of the decennial of the Phipps Dispensary for Tuberculosis.



discarded, because 132 were still in the sanatorium, and concerning 130 we had no data as to the result after discharge. There remained 141 patients of whose subsequent fate we had knowledge. Of these 141 the dead number 51, the living number 90. Of the 90 living, 44 are worse, 16 not definitely worse, 30 are better than when we first saw them.

That is, out of 141 cases, only 30 are improved and 111 are dead, worse, or not improved. Of the 39 apparently better, 4 had tubercle bacilli in the sputum. Of the 111, 47 had tubercle bacilli in the sputum.

It would not be reasonable to assume that all of the 130 patients concerning whom we had no data should be numbered with the improved. Should this unreasonable assumption be made, we would have 111 dead and worse, against 160 better. The results are all the more distressing when we consider that the period since discharge from the sanatorium has not been at all long.

Our conclusions derived from the observation of the patients in our clinic, are that in great part the cause of this poor showing lies in the premature dismissal of patients, especially when these belong to the poorer classes. We recommend a one or two years' residence for early cases, an indefinite stay for active cases, and the privilege of readmission for relapsed cases. We are especially opposed to any predetermined routine of length of residence, and urge an individualization. No patient should be discharged until he seems able to make a living for himself and family without danger of relapse.

#### DISCUSSION.

DR. HENRY BARTON JACOBS: It would be very unfortunate if this large group of students were to go away from here to-night thinking that the problem of tuberculosis from a social standpoint was not progressing. It certainly is. The best statistics we can gather are from Massachusetts, New York and Pennsylvania, and in these states in the ten years since the dispensary opened the mortality from tuberculosis shows distinctly a fall of from 40 to 50 per cent. What factors have brought this about may be open to question, but that tuberculosis is on the decline there can be no doubt.

The whole tuberculosis movement has been an hygienic movement. Rural living, suburban residence, the extension of trolleys into the country, all have come about largely since the tuberculosis problem has been under discussion. The desire for better housing, cleaner streets and better sewerage all goes hand in hand with the tuberculosis movement. To what extent the direct attack upon tuberculosis itself is responsible for the fall in the death rate, one perhaps cannot determine, but, as I say, the whole hygienic movement seems to be more or less dependent upon the incentive it originally received from the idea that tuberculosis can be cured if it be given a chance. If then this be the result of the crusade against tuberculosis, that the death rate in the best communities has been halved, certainly we should take courage to continue the fight.

The question of the number of cures in sanatoria or hospitals is one I have studied for a good many years. The more we learn about the cases discharged, the more we are inclined to believe in figures such as Dr. Wolman has presented. Still while only 30 saved out of 300 may seem to be poor results, probably these 30 would have died, too, had it not been for the sanatorium; and if one estimates conservatively the value of a human life, these 30 may have paid the expenses of that sanatorium for the year.

I have had largely to do with the Eudowood Sanatorium, and in the course of the years we have come gradually to the opinion

which Dr. Wolman has expressed, that it is more economical to wholly cure a case than to half cure it. There is no economy in sending a patient away before he is ready and then having to take him back time after time. So that the policy of the Eudowood Sanatorium is to keep its patients until one thing or the other happens, either they are well, or they die.

At Eudowood we have arranged an "after cure," as it were, something which should be found in connection with all sanatoria, namely, a place where a patient, when he is seemingly well and yet not sufficiently well to withstand home conditions without danger of relapse, can stay for a time until fully recovered, and where he can work on the farm, care for chickens or rabbits until he is so thoroughly well that the danger of relapse after return to home and work is reduced to the minimum. We feel that this department has great economical value.

This question of length of stay has been raised at the State Sanatorium also. There the same conclusion is being arrived at, that in the future it is going to be wiser and more economical to keep patients for longer periods than in the past, so that the State Sanatorium, with its 400 beds, will probably follow the policy which Reisterstown and Eudowood have adopted.

What more can be done in Maryland? Although not apropos of the topics discussed, I want to say a word of the great problem we face in this state in regard to tuberculosis among the negroes. It is an ever-present topic and one full of seriousness, with 100,000 negro people in our midst especially susceptible to tuberculosis, mingling with the families of all our people, cooking, washing, serving and nursing the children. If any individual in the community is likely to be the carrier of infection, it is the negro. He is apt to be careless, ignorant and unappreciative, and so a menace not only to himself and his people, but also to the community in general. We are planning to attempt legislation in the coming winter to meet these conditions. Thus far there are no provisions in this state either for the incipient or the advanced case of tuberculosis among the negroes, except some 50 or 60 beds at Bay View, which are primarily reserved for pauper cases.

I wish to repeat what I said in the beginning: it would be very unfortunate for you to leave here to-night with the impression that the workers in the anti-tuberculosis crusade were discouraged, or were in any degree less enthusiastic in their work. While perhaps unduly hopeful of immediate results in the early days, they are still convinced that the disease can, under proper and sufficient methods and facilities, be continuously diminished in any community with much suffering saved and many lives restored to health and usefulness. Whether it can be wholly eradicated in the future is problematical, but, with the encouraging results already obtained before us, we cannot for one moment think of remitting our efforts to bring about this most desired end. Every one should put his shoulder to the wheel and give the best strength in him to this cause. You students who are going from here into many different communities in many parts of the country should aim to make yourselves strong, vital factors in this war against a disease which is destroying more men and women each year than all the fighting armies of Europe combined.

DR. J. HALL PLEASANTS: The development of local institutional care of the tuberculous is interesting as we look back over the past 10 years. The movement really started at Eudowood several years before the Phipps opened, and for the first few years all classes of patients were taken there. As soon as the point of view which Dr. Hamman emphasizes was generally accepted Eudowood began to seek only early cases. Then followed soon afterwards the development of the State Sanatorium, at first largely devoted to the care of early cases. Later at both institutions emphasis was also laid upon the care of advanced cases, showing the tendency to look at the problem from the community standpoint rather than from the standpoint of the individual.

I think it might be interesting to some of you to know what



the institutional facilities are at present for the care of the tuberculous in Maryland. There are approximately 800 beds for Maryland, and of that number something over 500 are available for the tuberculous patients from Baltimore. The State Sanatorium can now handle 450 patients; about one-half of these coming from the counties, and the other half from the city. Eudowood has 100 beds and Bay View slightly under 200. There are accommodations at the Hebrew Hospital for about 55 patients. These are the four important institutions of the state. Over one-half of the beds for city patients are open to the poor of Baltimore, and are paid for, either in whole or in part, by the city. A good deal of money is expended and, of course, it is important to get the very best results. The funds available for the purpose are limited. The amount spent annually by the city and by the state is upwards of \$200,000, and this sum does not include the cost of new construction. This is a large expenditure and, on the whole, is spent wisely. Perhaps it is just as fortunate that we have not tried to go ahead quite so rapidly as at one time we hoped to do before the situation was so thoroughly understood as it is now.

There are at present not sufficient accommodations for negroes and certain other classes of cases from Baltimore. On the other hand, to a certain extent, what can perhaps be spoke of as "the unstimulated demand" has already almost been met. If we want to encourage more patients to enter the hospitals we must give them better hospitals and better care than are offered by some of those now in existence. At Bay View, for instance, I doubt very much if we could get many more patients in a hospital of the character which we now have, even if we had more beds, as a certain stigma is still attached in the minds of the people to an institution very closely associated with an almshouse. On the other hand, if we had a municipal hospital of a distinctly better grade, offering better nursing care and greater physical comforts

than can be obtained at some of the hospitals now receiving cases from Baltimore, we could get a larger number of patients to enter it. If all of the hospitals would readmit patients, I think the call for additional beds would be considerably increased. It is a difficult problem, and we seem to be going slowly; yet when we look back over the 10 years covered by Dr. Hamman and by Dr. Wolman we see that a good deal has actually been accomplished in providing hospital care.

DR. WOLMAN: I hate to take up any more time, but there is one statement I do not like to pass by, even from a friend, and that is that there are enough beds to meet the demand. This is true only with the vicious system we now have of not keeping patients long enough, which should be kept in mind. If the patients are kept long enough, we shall not have enough beds.

DR. JANEWAY: In summing up the results of the tuberculosis work here, I think we all feel that The Johns Hopkins Hospital owes a great deal to Dr. Hamman for the work that he has done in developing the Phipps Dispensary during these 10 years and for the kind of scientific publications that have appeared. The organization of the work and the men that he has brought together on the staff of that institution are things of which he should be very proud. In particular, I think we should recognize how important Dr. Hamman has made himself and how exceedingly valuable he has made his opinion in all tuberculosis matters, as the result of his 10 years' work in this branch of the hospital.

We now look forward to a new period and I hope you all feel that the Laennec Society is a place where you actively participate in the tuberculosis movement, which is now entering upon a somewhat new phase and in which the educated physician is to play an increasingly important rôle. It is therefore incumbent upon all of us to become educated physicians in respect to the attack on the problems of tuberculosis.

## CONCERNING THE OCCURRENCE OF TUBERCLE BACILLI IN THE CIRCULATING BLOOD.

By C. R. AUSTRIAN and LOUIS HAMMAN.

### I. INTRODUCTION.

Examination of the bodies of individuals dead of pulmonary tuberculosis or of other localized tuberculous disease almost constantly reveals tubercles scattered through organs and tissues other than those predominately affected. These tubercles are usually few in number and in an early stage of development. Their location justifies the assumption that as a terminal event in tuberculous disease tubercle bacilli invade the blood stream. Likewise, the obvious details of miliary tuberculosis can be explained only by accepting that under favorable mechanical conditions the blood is suddenly surcharged with tubercle bacilli. These well-established observations have been universally confirmed, but pathological anatomy offers no facts to prepare us for the astonishing results of more recent bacteriological investigations which would persuade us to believe that a bacillemia constantly accompanies tuberculous infections. Indeed, our credulity is taxed to this extreme, namely, we are told that tubercle bacilli occur in the blood not only of the manifestly tuberculous, but also of those with latent tuberculous foci, not singly, but in large numbers.

It is unnecessary to comment upon the violence these claims do our established notions about tuberculosis. They are revo-

lutionary and demand a complete change of our fundamental views upon the nature of tuberculous infection and the course of tuberculous disease. Besides, they have received wide recognition and at present figure prominently in the arguments and generalizations that adorn tuberculosis literature. Therefore, it is important critically to review the data upon which these claims rest, and to furnish additional evidence that may aid to solve the difficulty.

We will review the situation briefly and in outline, since a number of excellent and detailed accounts of the numerous pertinent investigations have but recently appeared.<sup>1</sup> Shortly after the discovery of the tubercle bacillus many pathologists demonstrated acid-fast organisms in the blood of corpses dead of miliary tuberculosis, and a little later clinicians occasionally found them during life in the blood of patients suffering from the same disease. This discovery caused no surprise, for the facts only confirmed established views about the nature of miliary tuberculosis. Indeed, before the discovery of the tubercle bacillus, Villemin had successfully inoculated animals with the blood of tuberculous bodies, and Baumgarten had con-

<sup>1</sup> Elsässer; Rothacker and Charon; Berry; Haas; Klemperer; Hage; Klopstock and Seligmann.



firmed these results with the method of inoculating into the anterior chamber of the eye. However, it was generally conceded that, although tubercle bacilli invade the blood stream in miliary tuberculosis, still in local tuberculous infections no bacillema occurs, and that even in advanced stages of pulmonary tuberculosis tubercle bacilli are carried by the blood only intermittently and in small numbers. The first communication to ruffle the settled calm of this conviction came from Liebmman in 1891, who claimed that the blood of patients treated with tuberculin contains numerous tubercle bacilli, whereas he was unable to demonstrate them in the blood of patients not so treated. Attempts to confirm these results failed, and Kossel ended the dispute when he was allowed to examine Liebman's slides, and pronounced his results to be due to faulty technic.

After this demonstration, interest in the occurrence of tubercle bacilli in the blood subsided, and during the following 15 years was only occasionally aroused. Thus Jousset, in 1904, by the method he names inoscopy, found tubercle bacilli in the blood of 11 out of 35 cases of pulmonary tuberculosis. Other French observers with the same and similar methods corroborated these results, but animal experiments, that is, injecting the blood into guinea pigs, gave a much lower percentage of positive findings. For instance, Bergeron found only 2 positive of 36 examined; Gary 5 out of 35. In Germany Lüdke's results attracted attention; by injecting intraperitoneally into guinea pigs from 5 to 10 cc. of blood withdrawn from the arm vein of tuberculous patients, 5 of 17 animals developed tuberculosis. Liebermeister, in 1909, reported examining the blood of 50 cases of pulmonary tuberculosis by inoculating guinea pigs intraperitoneally and thus demonstrating tubercle bacilli in 20. Although most of the patients had far-advanced pulmonary disease and many were examined shortly before death, still these results stand so prominently in contradiction to the experience of other investigators that they will receive further notice.

In this country interest was rudely awakened by the reports of Rosenberger. In 1909 this investigator published his results of the microscopical examination of the centrifugalized sediment of citrated blood from 49 cases of tuberculosis in all stages, claiming to have discovered tubercle bacilli in every instance. In a later report the number is increased to 300, all positive. This startling announcement led at once to control investigations here and in England, with the result that similar experiments undertaken upon tuberculous individuals and tuberculous cattle failed completely to verify Rosenberger's claims. The corroboration of Forsyth in England and Marshall and Petty and Rogers and Murphy in America furnishes isolated differences from the general testimony. The source of these conflicting results received a satisfactory explanation when Brem, followed by many other workers,<sup>2</sup> demonstrated the frequent contamination of distilled water with acid-fast bacilli. Since then opinion in this country has remained unshaken, and until recently no investigations of importance have been added to the subject.

During the same period extensive researches were being pursued in Germany which led to widely varying results, and these researches continuing actively to the present time have given rise to a vigorous polemic. In 1908 Staübli introduced the acetic-acid method for examining the blood for organisms and during the following year Schnitter further improved the procedure by adding antiformin digestion. Subsequent investigations have been carried out almost entirely by the acetic-acid-antiformin method, a method, although tedious in detail,

Year.	Author.	Microscopically.		Animal inoculation.	
		Number of cases.	Per cent positive.	Number of cases.	Per cent positive.
1909	Schnitter.....	38	32	...	...
	Rosenberger.....	300	100	...	...
	Lippmann.....	25	44	...	...
	Liebermeister.....	...	...	50	40
1910	Jessen and Rabinowitsch..	36	28	...	...
1911	Kurashige.....	155	100	...	...
	Sturm.....	50	22	50	46
	Krause.....	132	25	...	...
	Kennerknecht.....	68	100	13	100
1912	Susuki and Takaki.....	517	98	...	...
	Rumpf.....	43	67	35	8
	Hilgermann and Lössen...	64	25	...	...
	Bacmeister and Rueben...	?	100	15	0
1913	Nobecourt and Darre.....	...	...	40	10
	Liebermeister.....	100+	48	...	...
	Klemperer.....	14	86	...	...
	Bogasau.....	41	5	41	0
	Fraenkel.....	51	10	51	14
	Krabel.....	35	57	...	...
	de Verbizier.....	15	0	15	0
	Rogers and Murphy.....	50	100	...	...
	Bernard et al.....	36	11	...	...
	Rist et al.....	50	14	50	0
	Lange and Lindemann....	78	0	...	...
	Rothacker and Charon....	...	...	46	2
	Elsässer.....	41	7	15	0
	Querner.....	...	...	37	0
1914	Faginoli.....	81	100	...	...
	de Amicus.....	...	...	30	0
	Fraenkel.....	18	22	25	8
	Moewes and Bräutigam...	30	0	50	0
	Rueben.....	24	100	13	0
	Kachel.....	26	35	26	15
	Brandes and Mau.....	40	45	...	...
	Mayer.....	25	20	25	0
	Baetge.....	38	0	46	37
	Fisher.....	13	0	13	0
	Haas.....	24	46	24	0
	Klopstack.....	49	18	49	0
	Lehmann.....	...	...	104	6
	Berry.....	51	0	...	...

still simple in conception. The accompanying table shows at a glance what results have been obtained. The table is not constructed with any pretense to completeness, but with the desire to illustrate briefly and strikingly the divergence of the results. As may be seen, investigators differ to this extreme, whereas some find tubercle bacilli in the blood of all patients with tuberculous disease, be it early or advanced, others fail to find them even in the most advanced stages of the disease. Between these extremes there is every grade of difference. A few authors push the matter to the apparently ridiculous length of finding tubercle in the blood of individuals with latent tuberculous lesions and Kurashige to the inconceivable

<sup>2</sup> Holmes; Beitzke; Lehmann.



point of claiming to diagnose a fresh tuberculous infection by the presence of bacillema even before the development of tuberculin hypersensitiveness as manifested by cutaneous reactivity.

It is needless to review the many possible sources of error in examining blood preparations for tubercle bacilli. The matter has received repeated and extended consideration.<sup>3</sup> These possibilities are acknowledged by those who find tubercle bacilli most frequently, for they claim to have employed a scrupulous technic specifically to guard against this error. However, in view of the many negative results published by experienced and careful investigators, one is justified in assuming an attitude of skepticism towards positive microscopical findings, at least so far as to demand that the burden of proving the identity of the acid-fast organisms or particles found shall rest upon those who claim to discover tubercle bacilli so constantly in the blood.

The results of animal experiments cannot be so lightly disregarded. What this method of investigation has revealed is also shown in the table, and a glance discovers that the positive findings fall far below the proportions established by the microscopical method. However, the variation between the results of individual observers is hardly less astonishing. One author obtains constantly positive results, another in nearly half his cases; whereas many are able to demonstrate the presence of tubercle bacilli only occasionally even in advanced stages of tuberculous disease. The methods employed are reasonably uniform, consisting commonly in the intraperitoneal injection into guinea pigs of from 1 to 5 cc. of blood immediately upon withdrawal from the patient. Some have employed the sediment of from 1 to 10 cc. of blood treated by various methods of digestion, usually the acetic-acid-antiformin method; some, instead of inoculating intraperitoneally, have preferred subcutaneous injection into the groin. However, these procedures should in the main give generally comparable results and do not, taken alone, explain the existing discrepancy. Inoculation tuberculosis is a reasonably concrete and well-defined manifestation, for although certain confusing conditions do occur, still with care they may be differentiated from tuberculosis and they are not encountered frequently enough to be a satisfactory pretext for ignoring positive findings. When an author of experience states that so many inoculated animals developed tuberculosis, one cannot, in the absence of specific details, go behind the return and question the interpretation. The result must be credited, no matter how much at variance it stands with the experience of another, until more extended work decides the dispute. However, some authors do speak generally and some in detail about their animal results and upon these we may venture to comment.

A number of these authors disregard pathological-anatomical data and are content to diagnose inoculation tuberculosis in the absence of anatomical lesions when they find tubercle bacilli (we had better say acid-fast bacilli) in the sediment from the digested organs of the inoculated guinea pig.<sup>4</sup> In-

deed, some animals are labeled tuberculous because in turn tubercle bacilli are found microscopically in their blood. Certain authors go still further and rest the diagnosis of inoculation tuberculosis upon finding Gram-positive rods and Much granules in smears from organs and in the sediment of organs digested with antiformin.<sup>5</sup> Excluding the results thus acknowledged to have been won by methods which are obviously unreliable, there stands out still in contrast with the results of many other observers the high positive proportion of Liebermeister. Liebermeister's report is a lengthy one, with full protocols, and the work therefore is open to inspection. For the details of a criticism of his experiments we refer you to the comments made by Kahn. Kahn points out that none of Liebermeister's results are controlled by histological examination; that in some instances the diagnosis of tuberculosis rests solely upon the discovery of acid-fast rods in smears of the organs, for instance, in one animal that died two days after inoculation; that his description of lesions lacks precision, for in some instances he calls the lesions tuberculous because smears show acid-fast rods, while in other instances the same lesions are pronounced not tuberculous because smears fail to reveal tubercle bacilli; that in some animals that died shortly after inoculation, in one instance on the sixth day, he describes caseous areas at the point of inoculation, a result hardly possible unless the animal had previously had tuberculosis. Kahn's points are well taken, and they encourage the conviction that Liebermeister has diagnosed too leniently.

It is apparent from the table that the microscopical method has far more positive results than the method of guinea pig inoculation. Fischer has collected from numerous reports 3495 cases examined microscopically with 44 per cent positive results, whereas, a similar collection of 1250 cases examined by animal inoculation yields but 17 per cent positive. Those authors who are convinced of the accuracy and reliability of microscopical examinations have sought to meet this difficulty with ingenious explanations. Their arguments may be briefly summarized as follows:

1. Only a small number of tubercle bacilli are present in the blood, and although these may be found microscopically, still they are not numerous enough to infect a guinea pig.
2. The tubercle bacilli present in the blood are weakened, that is, they have so far lost their viability that they can no longer infect.
3. When the blood of tuberculous individuals is injected into guinea pigs, not only tubercle bacilli but immune bodies as well are introduced. The immune bodies inhibit the growth of the tubercle bacilli and prevent infection.

We have neither the space nor the inclination to enter this field of abstract speculation. It would be difficult to prove or disprove arguments 2 and 3, but what evidence we possess does not strongly favor them. As regards the first argument, our own experience (and the experience of many others) leads us to believe that the guinea pig is a more delicate indicator of the presence of tubercle bacilli than the microscopical examination of the sediment of much manipulated blood. But

<sup>3</sup> Hage; Fischer; Kahn; Gobel; de Amicus; Bogasau; Rumpf; Frankel.

<sup>4</sup> Kennerknecht.

<sup>5</sup> Sturm.



anyone interested may read the arguments for, in Klemperer and Liebermeister; against, in Kahn and Fischer.

As one would presume, the conflicting evidence concerning the occurrence of tubercle bacilli in the blood of human beings has led many investigators to seek more reliable data from animal experiments. However, in this direction one is immediately met by the difficulty of reproducing analogous conditions. Leaving aside the miliary form, tuberculosis in human beings is relatively a local disease during the greater part of its course. In animals it is difficult to regulate the conditions of infection so as to imitate this important feature of the disease in man. Following intravenous inoculation, the usual procedure for rabbits and guinea pigs, the tuberculous lesions predominate in the lungs, but the disease is seldom restricted and even early in its course other organs, notably the spleen and liver and kidneys, are extensively involved. Thus conditions more nearly parallel general tuberculosis than the local types usually found in man. The result does depend somewhat upon the infecting dose, for the same culture administered in large quantity may produce a rapidly fatal general infection, whereas, when a small amount is given, only scattered foci appear in the lungs and the animal may live for months. Under the former conditions one would expect to find tubercle bacilli in the blood constantly, whereas under the latter they might appear infrequently and demonstrably only towards the end of the disease. Results that we shall give later confirm this supposition. The virulence of the organism is likewise of importance. As Hess has shown in his interesting experiments, virulent types remain longer in the blood and reappear earlier than less virulent types. One is prepared, therefore, to find great divergence amongst the results obtained upon animals, and the expectation is fully confirmed by published reports. Tuberculous disease in cattle is somewhat nearer the human type than experimental infections in rabbits and guinea pigs, and examination of the blood of tuberculous cattle has yielded almost uniformly negative results.<sup>6</sup>

Although many isolated investigations upon the infectiousness of the blood of tuberculous animals had previously been made, the first extensive report upon the subject appeared in 1907 from Marmorek. He found that after subcutaneous inoculation of guinea pigs tubercle bacilli appear in the blood from 30 to 60 days later; after inoculation into the anterior chamber of the eye somewhat earlier; and still earlier after intraperitoneal inoculation. Injected into the arterial blood stream tubercle bacilli disappear from the blood in from 1 to 2 days to recur 5 to 14 days later; injected intravenously they disappear in from 1 to 2 hours to recur from 2 to 6 weeks later. Hess confirms these results in part, since he finds that virulent organisms remain in the blood from a few to 27 hours after intravenous injection and that they then disappear to return again 4 to 5 weeks later when the animal has become extensively tuberculous. The occurrence of tubercle bacilli in the blood has been investigated upon animals just as upon human

beings, both microscopically and by guinea pig inoculation. Concerning the microscopical method, it need only be said that the same confusing results are obtained as were commented upon in considering the results of the method applied to human beings, namely, some claim to find them constantly, others in a large proportion of the animals, still others in healthy as well as in infected animals. The results obtained by guinea-pig inoculation are almost as confusing. No doubt the severity of the infection, the virulence of the infecting organism and the interval after infection that the examination is made explain much of the discordance.

Finally, we would point to the further confusion that Rabinowitsch has precipitated by renewing the claim that tuberculin mobilizes tubercle bacilli. Although unable to demonstrate tubercle bacilli in the blood of tuberculous animals before tuberculin is given, she finds them frequently after the injections. Bacmeister confirms these results upon human beings. Of 15 individuals whose blood was negative by animal inoculation, 4 became positive after a diagnostic tuberculin reaction. Mayer, Moewes, Liebermeister, Storath, Lange and Lindemann fail to confirm Bacmeister's results. Hage and Fischer have published extensive experiments upon animals and disagree with Rabinowitsch's conclusions.

## II. AUTHORS' RESULTS.

During the past two years the authors have been interested in the question of the occurrence of tubercle bacilli in the circulating blood, and since each has worked quite independently of the other, the results, which in the main agree, are therefore more strikingly confirmed. It is thought best to present the contributions separately and at the end to summarize the results and draw the conclusions that the work fully warrants:

### A. INVESTIGATIONS OF DR. CHARLES R. AUSTRIAN.

The work herewith briefly reported has been carried on through a period of some 20 months. It will be dealt with under two main captions:

1. Clinical—Experimental.
2. Experimental.

1. *Clinical—Experimental.*—The blood of 50 individuals with pulmonary tuberculosis was studied. Twenty of the patients were in Stage I of the disease; 15 were in Stage II, and 15 in Stage III. All of them showed, in addition to definite physical signs of pulmonary infection, tubercle bacilli in the sputum, or a positive tuberculin reaction and in many both examinations gave positive results.

Specimens of blood obtained by puncture from a vein in the antecubital fossa, or forearm, were studied according to the following methods:

#### (a) Stained Preparations:

Five cubic centimeters of blood aspirated in a sterile syringe (Record) from a vein of the forearm were placed in a sterile flask containing 10 cc. of 3 per cent acetic acid and shaken thoroughly, avoiding the formation of foam. The mixture was allowed to stand for 30 minutes and was then decanted into

<sup>6</sup> Schroeder and Cotton; Sawyer; Broll; Mohler; Titze, Thieringer and John.



2 sterile centrifuge tubes and centrifugized for 45 minutes at the rate of about 2500 revolutions per minute. The supernatant red fluid was then removed; to the sediment 5 volumes of 33 per cent antiformin were added and after standing for from 1 to 6 hours the preparation was shaken until clear. Doubly distilled water was now added and the suspension was rotated for one hour at 2500 revolutions per minute. The white sediment, washed 3 times with doubly distilled water, was then spread on two new glass slides that had been thoroughly cleaned with alcohol and sterilized by dry heat. The spreads were fixed by heat in a sterile Petri dish, dried in the thermostat and stained by the Ziehl-Nielson method.

It is important to emphasize that extreme care was taken in cleaning all glassware employed. Flasks were boiled with alkali, washed with distilled water, alcohol and ether and sterilized by dry heat.

For the sake of brevity, suffice it to say that careful examination of such preparations made from the blood of 25 patients with manifest pulmonary tuberculosis in no instance revealed the presence of the tubercle bacillus. This in spite of the fact that the slides were each examined for from one to two hours, the fields slowly searched with the aid of a mechanical stage.

In only a few instances were a few acid-fast granules found and these could not have confused an observer familiar with the morphology or the staining properties of the bacillus tuberculosis.

These negative findings so at variance with the results of numerous observers led to the use of the method of inoculation with the idea that it might prove more delicate.

*Technic.*—(a) From a vein of the forearm 10 or 15 cc. of blood were aspirated into a clean sterile Record syringe and immediately mixed with 1.5 to 3 cc. of sterile 1.5 per cent sodium citrate solution to prevent coagulation.

From 4 to 7.5 cc. of the citrated whole blood were injected into the peritoneal cavity of a guinea pig. After six or eight weeks the animal was etherized and examined for evidences of tuberculous infection.

This procedure was carried out in 25 cases with completely negative results.

(b) Ten or 15 cc. of blood obtained according to the method described above were defibrinated by shaking with sterile glass beads. Inoculation experiments made with blood so prepared were carried out with specimens obtained from 15 cases of pulmonary tuberculosis. In not one of the inoculated guinea pigs was any sign of tuberculous infection found.

(c) The intraperitoneal injection into guinea pigs of varying quantities of serum, obtained from tuberculous individuals likewise failed to cause infection.

(d) The intraperitoneal injections of the antiformin insoluble residue of 10 or 15 cc. of blood from infected patients did not lead to the development of tuberculosis in the animals.

Pulmonary tuberculosis in man is generally a localized infection and to obtain from an examination of the blood of animals data comparable to the facts furnished by the study of human blood, the attempt was made to produce a similar localized pulmonary infection in animals. This was readily

accomplished by the use of Meltzer's method of intratracheal injection.

II. *Experimental Part.*—Rabbits weighing from 1700 to 2800 gm. were chosen.

The rabbit was etherized and placed on its back in such a position as to permit extension of the neck over the end of the operating board. The mask was then removed, a gag placed in the mouth and slowly, gently, a fine rubber catheter was passed through the mouth into the trachea. To facilitate the passage of the tube a close-fitting copper wire tipped with a blunt lead was kept in the catheter and this was not withdrawn until a proper insertion had been obtained. Evidence of the entrance into the trachea was furnished by reflex cough and apnea; and by the grating of the lead tip along the tracheal rings, the hand recognized the passage of the sound within the trachea.

When the catheter was in place the wire was withdrawn and a sterile syringe partly filled with material for injection fixed to it. Transmission of a wave through this fluid with each respiratory phase, again confirmed the position of the tube. Under slight pressure the material for injection was now slowly introduced.

In the following experiments suspensions of tubercle bacilli A1 and H39 in 0.85 per cent salt solution were employed:

A1. *A Bacillus Tuberculosis of Avian Type.*—This organism was obtained four years ago from an outside source and was fully identified as of the avian variety. It grew rapidly and luxuriantly on glycerine agar and was of only slight virulence.

H39. *A Bacillus Tuberculosis of Human Type.*—The culture was obtained from the Saranac Laboratory through the kindness of Dr. Allen Krause—a typical bacillus tuberculosis, typus humanus, and of constant virulence.

The suspensions of these bacilli used in the experiments recorded below were prepared as follows:

The growth on a slant of glycerine agar was placed in a sterile flask that contained sterile glass beads, thoroughly shaken with 0.85 per cent salt solution until a fairly homogeneous suspension was obtained and this was filtered through sterile cotton to remove coarse clumps. This suspension was then diluted with 0.85 per cent salt solution until it was of the turbidity of a 36-hour broth culture of *Bacillus typhosus*. From 2 to 3 cc. of this material were injected into the trachea.

Thirty-six rabbits received intratracheal injections of one or the other strain. Six died from trauma received as a result of faulty technic in passing the catheter, 5 succumbed to intercurrent infection and showed no gross evidence of tuberculosis, and 25 developed pulmonary tuberculosis. In only 10 of the latter did a disseminated infection develop.

At varying intervals of from 2 to 5 days the blood of these animals was examined for the presence of tubercle bacilli. The methods employed were those above described in connection with the study of human blood—examinations of stained smears, inoculations into guinea pigs of citrated whole blood, of blood defibrinated by whipping and of serum. The quantities of blood used in these tests varied from 5 cc. aspirated from the heart by punctures to the entire blood content of the rabbit.



In four instances all of an animal's blood was utilized in making smear preparations on two slides. In four other experiments the blood of one rabbit was injected into the peritoneal cavities of two guinea pigs. In every case a complete autopsy was made of the donor of blood for smear preparations or for reinoculation experiments, and the anatomical findings are here briefly presented.

The following types of lesions were found:

(a) A gelatinous lobar pneumonia in gross resembling the variety occasionally seen in man.

(b) A diffuse caseating broncho-pneumonia at times causing a pseudolobar consolidation.

(c) A combination of these two varieties.

(d) Extensive cavity formation in the lungs.

Although bacilli of low virulence were given in small numbers to resistant animals, a typical fibroid phthisis was never produced.

Following inoculation the rabbits generally showed no symptoms for 10 days. Then cough developed, at first paroxysmal, later becoming more constant. Within a few days emaciation became evident and rapidly progressed until death occurred.

At autopsy 12 to 39 days after infection no constant localization of the lesions in any one of the lobes of the lungs was noted, though the maximum involvement was usually found in either or both lower lobes.

In general the affected lung was more voluminous than the normal, often encroaching upon the opposite side of the thorax. Outspoken pleural exudate was not seen in any of the animals, but a thickened pleura or irregular nodulation, due to subserous tubercles, was frequently found.

The lungs in several of the animals showed a typical gelatinous pneumonia. The diseased lobe or lobes voluminous, firm, non air-containing; on section, moist, translucent, gray, mottled in the earlier cases (before 12 days) with hemorrhagic dots, in the later ones (after 18 days) dotted with small yellow caseating areas. The bronchi were usually filled with a grumous yellow exudate. With such a condition in one lobe of a lung an entirely differently appearing lesion was found in other portions of the same lung or in the opposite one. Either emphysema with areas of grayish red (early) or of caseating (late) broncho-pneumonia, or congested parenchyma with scattered miliary and confluent tubercles, was frequently present.

Instances of bilateral lobar or pseudolobar tuberculous broncho-pneumonia were frequent.

Cavity formation was found in 10 animals, the vomicae varying in size from several millimeters up to that of an entire lobe. Generally they were multiple, honeycombing the entire pulmonary tissue. The walls were ragged and irregular, the contents typical caseous material. No eroded or isolated blood vessels were found, nor could secondary infection be demonstrated, even when communication of a cavity with a bronchus was apparent.

Microscopic examination of the lesions showed the following:

The alveoli were densely packed with leucocytes, the pre-

dominant type varying in different areas. In some there were many polymorphonuclears and relatively few mononuclears; in others the converse was true. Again, many contained numerous mononuclear leucocytes, large mononuclear endothelial cells and multinucleated giant cells. Many alveoli were loosely filled with a granular detritus, mononuclear leucocytes and red corpuscles.

The alveolar walls in many places were denuded of endothelium and the interalveolar vessels were congested.

In areas, the architecture of the lungs was completely destroyed, replaced by caseous material; or mere tags of alveolar walls remained. Necrosis apparently began in the exudate and spread from there, involving the lung parenchyma and the bronchi.

Typical tubercles fresh and in various stages of degeneration were numerous.

In places beginning repair was seen.

The bronchi in many places were dilated, their lumens containing an exudate rich in polymorphonuclear and mononuclear leucocytes, their walls in places ulcerated, the ulceration appearing to have spread from the alveoli.

The pleura showed thickening and infiltration with mononuclear leucocytes.

Tubercle bacilli were fairly numerous throughout the lesions.

In the 10 instances in which disseminated tuberculosis developed a few small tubercles were found in the kidneys and spleen.

It is interesting that in the series of experiments no one type of lesion was found at a constant time after infection, a variety that occurred early in one animal developing late in another, and vice versa.

The findings here recorded agree closely with those described by Lewis and Montgomery in their experiments dealing with bronchogenic infection of dogs with the tubercle bacillus, except that they did not find the development of a gelatinous pneumonia.

The results of the examination of the blood of the rabbits with localized pulmonary tuberculosis completely confirmed the findings obtained from the study of human blood already recorded. In none of the 15 rabbits in which the infection remained a local one were bacilli demonstrated in the circulating blood by the use of any of the methods described.

In 3 of the 10 animals that developed a systemic infection, tubercle bacilli were found in the blood. In one both stained smears and inoculation experiments gave positive findings; in one organisms were found in stained preparations, whereas a guinea pig injected intraperitoneally with blood remained free of tuberculosis; and in the third case the inoculation test was positive, though examination of stained smears failed to show the presence of any organisms.

#### B. INVESTIGATIONS OF DR. LOUIS HAMMAN.

1. *Clinical-Experimental.*—The blood of 24 patients with advanced pulmonary tuberculosis was examined for the presence of tubercle bacilli. The blood of two patients was examined twice, of another three times, a total of 28 examinations.



The patients all had far-advanced pulmonary tuberculosis; none had a lesion less extensive than Turban III, and all had well-marked local and general symptoms. Many of the patients were bedridden with high fever and night sweats at the time the examination was made. In all the diagnosis was confirmed by repeatedly finding tubercle bacilli in the sputum.

(a) *Microscopical Examinations*.—From 2.5 to 5 cc. of blood withdrawn from the arm vein were prepared by the Staübli-Schnitter method which has been outlined by Dr. Austrian. During the earliest investigations an elaborate process was followed in cleaning the glassware, subsequently only scrupulous cleanliness and hot air sterilization were used. Throughout the investigation only freshly distilled water was employed. The slides were examined on a mechanical stage and from one to two hours devoted to each specimen.

In not one instance was a single tubercle bacillus found. I make this statement positively, for in the examination of the slides I encountered no structures that left me hesitating about their identity; I mean about their being or not being tubercle bacilli. It is true that the first slides were the source of some little trepidation, since a few blue rods were seen which aroused fear, lest the method of treating the blood might destroy the characteristic staining reaction of the tubercle bacillus. This fear was promptly allayed when I found that tubercle bacilli added in small numbers to freshly drawn blood were recovered with unaltered staining properties after the blood had been passed through the usual routine.

(b) *Animal Inoculation*.—From 2.5 to 5 cc. of the blood of 20 of the patients above referred to were injected intraperitoneally into a guinea pig. Eight of the 20 animals died within 3 weeks after the injection, 6 of them, indeed, within 24 hours. Twelve animals lived for one month or longer. At autopsy none showed any lesion that could have been suspected of being tuberculous.

2. *Experimental*.—(A) Four rabbits were inoculated intravenously with a suspension of human tubercle bacilli in 0.85 per cent saline solution. The culture used was H39 previously described by Dr. Austrian.

Five cubic centimeters of blood were withdrawn from the heart in one instance after 5 hours; in another after 24 hours; in two instances after 19 days; in two instances after 44 days; in another instance after 45 days.

All four rabbits at autopsy showed extensive pulmonary tuberculosis and a few scattered tubercles in the spleen, liver and kidneys except one of the animals which died on the 24th day after inoculation and showed only pulmonary lesions.

In 5 of the 7 examinations the 5 cc. of blood were divided into two portions; 2.5 cc. were injected intraperitoneally into a guinea pig; 2.5 cc. were prepared by the Staübli-Schnitter method for microscopical examination.

In 2 of the 7 examinations the whole 5 cc. of blood were prepared for microscopical examination. Of the 7 microscopical examinations 2 were positive. In each instance 2 tubercle bacilli were found after prolonged search. One of the positive

examinations was made 44 days after inoculation, the other 5 hours after.

Of the 5 guinea pigs inoculated intraperitoneally none showed any evidence of tuberculous infection; 1 animal died 4 weeks after inoculation, 2 after 6 weeks, 1 after 14 weeks, and 1 was sacrificed after 3 months. The 2 specimens of blood positive microscopically were both negative by guinea pig inoculation.

(B) Three rabbits were inoculated intravenously with a suspension of human tubercle bacilli (H39).

Twenty-two days after inoculation 5 cc. of blood were withdrawn from the heart; 2.5 cc. were prepared for microscopical examination; 2.5 cc. were injected intraperitoneally into a guinea pig.

Subsequently the rabbits received increasing doses of tuberculin and the blood was examined at intervals for tubercle bacilli. From 5 to 15 cc. of blood were withdrawn from the heart; from 2 to 5 cc. were injected intraperitoneally into a guinea pig; from 2 to 10 cc. were prepared for microscopical examination.

Rabbit No. 5 was sacrificed 78 days after inoculation. Autopsy showed diffuse caseous and fibroid tubercles scattered throughout the lungs; no tubercles in other organs.

Rabbit No. 7 was sacrificed 77 days after inoculation. Autopsy showed about 10 firm caseous nodules about 2 mm. in diameter scattered through the lungs; several small tubercles in the liver and spleen.

The protocol of experiment No. 6 is given in detail as an illustration:

#### RABBIT No. 6.

February 5, 1914. Intravenous injection of suspension of human tubercle bacilli (Culture H39).

March 7. Five cc. blood withdrawn from the heart. Two and one-half cc. prepared by the acetic acid-antiformin method for microscopical examination. No tubercle bacilli found.

Two and one-half cc. injected intraperitoneally into guinea pig. Guinea pig sacrificed June 24. No evidence of tuberculosis.

March 18. Subcutaneous injection of 0.025 cc. bouillon filtrate.

March 19. Five cc. blood withdrawn from the heart; 2 cc. prepared for microscopical examination. No tubercle bacilli found.

Three cc. injected intraperitoneally into guinea pig. Guinea pig died March 28, 1914. No tuberculosis found.

March 24. Subcutaneous injection of 0.1 cc. O. T.

March 30. Subcutaneous injection of 0.2 cc. O. T.

April 1. Subcutaneous injection of 0.25 cc. O. T.

April 2. Eleven cc. blood withdrawn from the heart; 6 cc. prepared for microscopical examination. No tubercle bacilli found.

Five cc. injected intraperitoneally into guinea pig. Guinea pig sacrificed June 24. No tuberculosis found.

April 7. Intravenous injection of 0.5 cc. O. T.

April 8. Twelve cc. blood withdrawn from the heart; 7 cc. prepared for microscopical examination. No tubercle bacilli found.

Five cc. injected intraperitoneally into guinea pig. Guinea pig died April 17, 1914. No tuberculosis.

April 20. Intravenous injection of 1 cc. O. T.

April 21. Fifteen cc. blood withdrawn from the heart; 10 cc. prepared for microscopical examination. No tubercle bacilli found.



Five cc. injected intraperitoneally into guinea pig. Guinea pig sacrificed June 27, 1914. No tuberculosis found.

April 27. Intravenous injection of 1 cc. O. T.

April 28. Fifteen cc. blood withdrawn from heart; 10 cc. prepared for microscopical examination. No tubercle bacilli found.

Five cc. injected intraperitoneally into guinea pig. Guinea pig sacrificed June 27, 1914. A few small tuberculous nodules in the cmentum and spleen. Verified microscopically.

April 29. Intravenous injection of 1 cc. O. T.

April 30. Fifteen cc. blood withdrawn from heart; 10 cc. prepared for microscopical examination. No tubercle bacilli found.

Five cc. injected intraperitoneally into guinea pig. Guinea pig sacrificed June 27. Tuberculous nodules on peritoneal surface, in liver and in spleen. Tuberculosis in substernal lymph glands. Verified microscopically.

June 1. Rabbit extremely emaciated and moribund. Sacrificed. Extreme tuberculosis of the lungs, few scattered tubercles in the liver. Spleen normal. Microscopical sections showed extensive tuberculosis of the lungs. No tuberculosis in the spleen.

Rabbit No. 5 had six examinations of the blood. One was positive microscopically, one was positive by animal inoculation. The positive microscopical finding was on the 42d day after inoculation; the positive animal result on the 58th day.

The blood positive microscopically had no animal control; the blood positive by animal inoculation was negative microscopically.

Rabbit No. 7 had five examinations of the blood. All were negative, both microscopically and by animal inoculation.

Therefore, of 18 examinations of the blood of rabbits made from the 40th to the 86th day after inoculation with human tubercle bacilli, one was positive microscopically; three were positive by animal inoculation.

(C) Three rabbits were inoculated intravenously with a suspension of bovine tubercle bacilli (Culture B<sub>1</sub>) in 0.85 per cent salt solution. A liberal dose was given with the intention of producing a rapidly fatal infection.

Culture B<sub>1</sub> is a typical culture of the bovine type of tubercle bacillus of low virulence obtained from the Saranac Laboratory through the kindness of Dr. Allen Krause.

Rabbit No. 8 died on the 29th day after inoculation, immediately after bleeding. Autopsy showed extensive tuberculosis of the lungs and spleen, and numerous tubercles in the liver and kidneys. A rent in the right ventricle was the cause of death. On the 28th day after inoculation 5 cc. of blood were withdrawn from the heart. Two cc. were prepared for microscopical examination. No tubercle bacilli found. Three cc. were injected intraperitoneally into a guinea pig; the guinea pig sacrificed three months later showed extensive tuberculosis of the spleen and liver. On the same day the rabbit received subcutaneously 0.05 cc. O. T.

On the 29th day after inoculation 5 cc. of blood were withdrawn from the heart. Ten cc. were prepared for microscopical examination. No tubercle bacilli found. Five cc. were injected intraperitoneally into a guinea pig; the guinea pig died five weeks later and no evidence of tuberculosis was found.

Rabbit No. 9 died 31 days after inoculation. Autopsy showed extensive tuberculosis of the lungs and spleen and numerous tubercles in the liver and kidneys.

On the 28th day after inoculation 5 cc. of blood were withdrawn from the heart. Two cc. were prepared for microscopical examination; no tubercle bacilli found. Three cc. were injected intraperitoneally into a guinea pig; guinea pig died 49 days after inoculation and showed extensive tuberculosis of peritoneum, spleen, liver, substernal glands and lungs.

On the same day rabbit received 0.05 cc. O. T. subcutaneously.

On the 29th day after inoculation 15 cc. of blood were withdrawn from the heart. Ten cc. prepared for microscopical examination; one definite tubercle bacillus found. Five cc. injected intraperitoneally into a guinea pig; guinea pig sacrificed three months later showed extensive tuberculosis of spleen, tubercles in the liver and a few small areas of tuberculous infiltration in the lung.

Rabbit No. 10 died on the 37th day after inoculation. Autopsy showed extensive tuberculosis of the lungs and a small number of tubercles in the liver, spleen and kidneys.

Blood withdrawn on the 28th, 29th and 37th days after inoculation was negative upon microscopical examination; a guinea pig inoculated upon the 28th day died 18 days later and showed no evidence of tuberculosis; guinea pigs inoculated on the 29th and 37th days developed extensive tuberculosis of the spleen and liver.

Therefore, of 7 examinations of the blood of rabbits four weeks after intravenous inoculation with a large dose of bovine tubercle bacilli, one was positive microscopically, five were positive by animal inoculation.

(D) Three rabbits were inoculated intravenously with a barely opalescent suspension of bovine tubercle bacilli (Culture B<sub>1</sub>) in 0.8 per cent salt solution.

Rabbit No. 11, sacrificed 28 days after inoculation, showed at autopsy a number of firm tuberculous nodules scattered through the lungs and a few tubercles in the liver and spleen.

Rabbit No. 12, sacrificed 78 days after inoculation, showed numerous large caseous tubercles scattered through the lungs and a large spleen studded with tubercles.

Rabbit No. 13, sacrificed 28 days after inoculation, showed firm tuberculous nodules scattered through the lungs, but no tubercles in the other organs.

Upon these three rabbits 13 examinations of the blood were made during the period from the 14th to the 28th day after inoculation. During this period large doses of tuberculin were given intravenously. In each instance 15 cc. of blood were withdrawn from the heart; 5 cc. were injected intraperitoneally into a guinea pig; 10 cc. were prepared for microscopical examination. In no instance were tubercle bacilli demonstrated either microscopically or by animal inoculation. The protocol of experiment No. 11 is added.

#### RABBIT No. 11.

April 7, 1914. Intravenous injection of a suspension of bovine tubercle bacilli (Culture B<sub>1</sub>).

April 21. Fifteen cc. blood withdrawn from the heart; 10 cc. prepared by the acetic-acid-antiformin method for microscopical examination. No tubercle bacilli found.



Five cc. injected intraperitoneally into guinea pig. Guinea pig sacrificed June 24, 1914. No evidence of tuberculosis.

Intravenous injection of 0.025 cc. O. T.

April 22. Fifteen cc. blood withdrawn from the heart; 10 cc. prepared for microscopical examination. No tubercle bacilli found.

Five cc. injected intraperitoneally into guinea pig. Guinea pig died May 27, 1914. No evidence of tuberculosis.

April 27. Intravenous injection of 0.1 cc. O. T.

April 28. Fifteen cc. blood withdrawn from the heart; 10 cc. prepared for microscopical examination. No tubercle bacilli found.

Five cc. injected intraperitoneally into guinea pig. Guinea pig sacrificed June 27, 1914. No evidence of tuberculosis.

April 29. Intravenous injection of 0.2 cc. O. T.

April 30. Fifteen cc. blood withdrawn from the heart; 10 cc. prepared for microscopical examination. No tubercle bacilli found.

Five cc. injected intraperitoneally into guinea pig. Guinea pig died June 16, 1914. No evidence of tuberculosis.

May 4. Intravenous injection of 0.5 cc. O. T.

May 5. Fifteen cc. blood withdrawn from the heart; 10 cc. prepared for microscopical examination. No tubercle bacilli found.

Five cc. injected intraperitoneally into guinea pig. Guinea pig sacrificed June 27, 1914. No evidence of tuberculosis.

May 5. Rabbit sacrificed. Autopsy shows a few small firm nodules scattered throughout the lungs, and a few tubercles in the liver and spleen. Confirmed microscopically.

#### SUMMARY.

In pulmonary tuberculosis the authors were unable to demonstrate the presence of tubercle bacilli in the blood in a single instance notwithstanding the fact that many of the patients when examined were in the last stages of the disease.

In animals, when the disease remains localized in the lungs, tubercle bacilli are not found in the circulating blood. When the disease becomes generalized, as it does in the late stages of pulmonary infection and very soon after overwhelming intravenous injections, circulating tubercle bacilli are frequently demonstrable.

The evidence presented points strongly against the mobilization of tubercle bacilli by the injection of tuberculin.

A larger number of positive results was revealed by the method of animal inoculation than by the microscopical examination of the sediment obtained by treating blood according to the acetic-acid-antiformin method.

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## PROCEEDINGS OF SOCIETIES.

## THE JOHNS HOPKINS HOSPITAL MEDICAL SOCIETY.

MAY 3, 1915.

## 1. The Use of a Celluloid Tube in Adding Length to the Terminal Phalanx of a Finger, After Traumatic Loss of Tissue. DR. J. S. DAVIS.

When a partial traumatic amputation of the terminal phalanx of a finger takes place, one of two conditions is found: Either the part is cut away clean with little damage to the remaining portion, or the part is crushed off, and the tissues adjacent to the amputated portion are more or less traumatized. After the ordinary healing by granulation we often find a sensitive stump in which the bone is covered only by a thin scar.

The question arises as to the best method of early treatment, especially when the bone is exposed.

In order to obtain a good functional result we must contrive to place a pad of tissue over the bone. This may be done rapidly and satisfactorily by shortening still more the exposed bone and closing the soft parts over it, but this method gives a shorter stump.

In certain occupations the loss of all or a portion of the terminal phalanx of a finger is a matter of considerable economic importance to the skilled worker. It is often advisable to preserve the remaining length of the finger, and if possible to replace the loss of tissue, thus giving a more useful and less painful stump, and at the same time one which is less disfiguring.

After seeing a number of these cases, it occurred to me that some procedure might be devised by which this object could be accomplished. One should always replace the amputated portion unless it is too much traumatized, or unless a period longer than 3 or 4 hours has elapsed between the time of the accident and the first treatment. This procedure is attended with little danger and if the replaced portion does not regain its vitality it can be easily removed, and the building up process then inaugurated.

The advisability of tissue transplantation suggested itself at once, and the method of utilization of pedunculated flaps from the chest or abdominal walls to replace the loss was considered. However, this method can only be carried out in the hospital, as constant supervision of the patient is essential on account of the irksome position necessary.

The majority of the patients with these injuries are treated in the Out-Patient Department, so a method must be used which will give good results without the necessity of admission to the hospital.

The most promising procedure seemed to be that of stimulating the growth of granulation tissue on the end of the stump, and in some way to confine the growth to the desired size and direction.

In searching for means to accomplish this I thought that a stiff non-adhesive material which could be wrapped around the finger, would be satisfactory. After a number of experiments I found that sheet celluloid 1/200 of an inch thick would be best for the purpose. This material was transparent and could be cut in a pattern, which, when rolled, formed a tube adjustable to the size of the finger.

*Technic.*—The stump is painted with tincture of iodine. The shaped piece of celluloid, after being soaked in bichloride of mercury (1-1000) for a sufficient time, is sponged off with ether or alcohol. It is then wrapped around the finger and secured with narrow adhesive strips, thus making a tube which is slightly smaller at its free end than at its base. When the tube is properly adjusted it will hug closely the edge of the wound, and will gradually become larger until it impinges on the first interphalangeal joint. The celluloid may extend as far beyond the

finger tip as is needful, and in addition to its primary function it also serves as a splint for the finger and as a protection to the wound.

In cases seen early a blood clot is allowed to form in the tube. This clot serves as a scaffold for granulations. If the soft parts are lacerated and spread apart, they are gathered together and held in place by the tube.

In cases seen after the granulations have started, every effort is made to stimulate their growth, and to train this growth along the tube.

Any desired medication may be applied to the wound after the celluloid is in place, either by pouring it into the tube, or by packing the tube with gauze. The dressing in this way comes in contact with the wound, and is confined by the tube. A loose gauze plug is then placed in the mouth of the tube, and over all a small dressing, secured by a bandage.

*Summary of Cases.*—Fifteen cases. Males, 13; females, 2. Ages, 16 to 50 years. White, 13; Colored, 2. Occupation.—Operators on machines, 15. Etiology.—All were injured by machines. Situation.—Right forefinger, 5; left forefinger, 4; right middle finger, 2; left middle finger, 3; right thumb, 1. Duration of Lesion before coming under my care.—One hour to 26 days. Amount Lost.—From .75 cm. of the tip to the entire terminal phalanx. Amount Gained.—From .5 to 1.25 cm. Type of Lesion.—The nail was involved in all. In 2 there was some loss of tissue, the remaining soft parts of the terminal phalanx being mush-roomed out and badly crushed, although still attached to the finger by pedicles. In neither of these was the bone involved. In 13 the amputations were more or less clean cut, with little crushing of surrounding tissues, and in all of these the bone was involved. In 10 of these the lesion involved more of the dorsal than of the palmar surface. In 1 the skin was involved equally on both aspects of the finger, and in 2 the lesion involved slightly more of the palmar surface. Treatment.—The celluloid tube was used in all, in addition to stimulation. In 1, in addition to the above, small deep grafts were used to hasten healing. Duration of treatment.—Entirely healed after 10, 21, 24, 26, 28, 29, 30, 33, 34, 35, 36, 39, 45, and 66 days, with an average of 33 days. The cases taking the greater number of days before healing were those in which the wounds were seen late, and which were prevented from prompt healing in order to give more length to the stump. Results.—There is increase in length of the soft parts in all, and in four instances the X-ray showed slight increase in the length of the bone.

There is not a single painful stump in the series. The pad of tissue over the bone is quite movable, and soft in all. Voluntary flexion of the terminal phalanx is excellent in all, even when only a small amount of the phalangeal bone remained. The celluloid tube has also been used with success as a protective dressing for other lesions of the terminal phalanx, such as compound fractures, lacerations, etc.

*Remarks.*—The accident may be caused in many ways. In this series they were all caused by presses of one sort or another.

The tissue loss of the terminal phalanx varied from that of the soft parts only to that of the entire phalanx.

The lines of section were in varying directions, but the involvement was usually more on the dorsal than on the palmar surface.

There was no retraction of the edges, the sections being as though cut through a banana or a sausage.

The comparative value of the different fingers varies with the occupation, but it may be safely stated that the thumb, the index and the middle fingers are the most generally useful.

The method is simple, and the patient can return to his home at once, and do light work after a short time.



A very small gauze dressing around the celluloid suffices. Any jar on the end of the tube is transmitted to the finger behind the wound, much as is the case in an artificial limb, where the weight-bearing portion is not on the end of the stump, but on the normal tissue above it.

The granulations may be observed through the transparent celluloid without having to remove the tube.

There is sometimes sweating of the skin of the finger, if the tube is allowed to remain in place for longer than two or three days. The tube may be easily removed as it does not stick, and after cleansing, it may be replaced, or a fresh tube adjusted.

The thickness of the granulating area can be stimulated by various means. As the granulations grow, the epithelium from the skin edge also grows, and often it is difficult to prevent it closing over the stump before the desired length is obtained. In these instances the epithelial edges should be retarded with silver nitrate.

In some cases when the granulations are sufficiently advanced, it is advisable to cover them with small deep grafts, in order to give a more stable and quicker healing. It might have been better to have grafted more of this series.

The cases seen soon after the accident give the best results, as far as increased length is concerned.

Building new tissue on the end of the stump is slow, but in the end it will preserve the bone which remains, and cover it; and will also often add materially to the length of the stump. If the joint is uninvolved, even a short bit of terminal phalangeal bone will form the basis for a shortened terminal phalanx, which may be voluntarily extended and flexed, and can be used nearly as well as an intact terminal phalanx.

From the standpoint of function, increased length, and improved appearance, the results have been better than with any other method with which I am familiar.

#### DISCUSSION.

DR. SMITH: I have been very much interested in this work of Dr. Davis. These cases he has presented this evening would under ordinary circumstances have been treated in the dispensary with good results, but with a shortened finger. By this treatment, a finger practically normal in length has been obtained, which in some cases would undoubtedly mean the difference between efficiency and inefficiency at the patient's trade or employment.

Dr. Davis and his associates have been giving special attention to another class of cases with equally beneficial results. For example, those patients who have slow healing wounds and chronic leg ulcers, many of whom have been returning to the dispensary more or less regularly for months, and in some instances years. They form the uninteresting cases in whom no one has had any particular interest, with the result that they received more or less superficial attention. As soon as Dr. Davis began to study wound healing and took over this work, the results were most gratifying. Many of those old cases were completely healed, and the length of time required for the process in practically any case has been reduced to a minimum. That is efficiency, because it saves the time and the feelings of the patient, besides saving the time of the surgeons and also materials. To members of the working class, the saving of time alone is of great importance. I wish we could have the same efficient methods throughout our dispensary, for there is need of it. The superficial examination and routine treatment characterizing most dispensary work is altogether wrong.

#### 2. \* Lesions Produced by Arsenicals and Their Bearing on the Problem of a Specific Arsenic Therapy. DR. WADE H. BROWN.

\* To appear later in the BULLETIN.

MAY 17, 1915.

#### 1. Case of Interstitial Omental Hernia and Sarcoma of the Body of the Uterus in the Same Individual. MR. BENJAMIN TAPPAN.

The patient, a white woman, aged 53, married, was admitted to the gynecological service of The Johns Hopkins Hospital on December 2, 1914, complaining of bleeding from the vagina. There was no history of cancer or tuberculosis in her family, and in other respects also her family history was negative. In her personal history her general health was excellent. She suffered from frequent frontal headaches, had occasional attacks of indigestion and sometimes had palpitations of the heart. She had been married twice, but had had no children and no miscarriages. Twenty-five years ago she underwent an abdominal operation, in which she thinks her left ovary was removed. She had no trouble following the operation, except that after several years a small hernia appeared at the lower angle of the scar. This became about as large as a hen's egg and remained stationary in size ever since. It had never at any time given her any trouble and had never been tender or painful. Twelve years before admission the patient was operated upon for hemorrhoids, with relief of the condition. The patient's menses appeared at the age of 12 and continued regularly and with no pain until her menopause, which occurred ten years before her admission to the hospital, at the age of 43. Since then she had had no bleeding at all until her present illness.

Her present illness began a little over a month before her admission to the hospital. She had had for some weeks a leucorrhœa, which was becoming gradually more profuse. One month before her admission she noticed bleeding from the vagina. This bleeding, the first since her menopause ten years before, was never severe. There was only a little bleeding from day to day, just enough to soil her linen. At this time her leucorrhœa became more profuse. She had no other symptoms; her appetite remained good, she felt well and had lost no weight. Her physical examination on admission showed her to be a well-nourished, healthy looking woman. Her lungs were negative. Her heart was slightly enlarged to the left, but there were no murmurs. On the abdomen there was a mid-line scar below the umbilicus, which was well healed, except at its lower portion, where there was a small protrusion, the size of a hen's egg. This protrusion was soft and fluctuant and increased slightly in size when she stood up. It was not tender and never gave her any pain. In other respects her abdominal and general physical examination was negative. The clinical examinations were negative. Vaginal examination, done under anesthesia, just before operation, showed normal external genitalia and vagina. The cervix was high in the vault, small and slightly lacerated. The uterus was normal in size, anteflexed and freely movable. There was no point of induration and no masses were felt. The adnexa seemed free.

She was operated upon on December 5 by Dr. Thomas S. Cullen at The Johns Hopkins Hospital. A curettage was done and the tissue fragments examined under the microscope. The diagnosis of carcinoma was made. The old abdominal scar was first resected. The small hernial sac was opened and proved to be a tri-locular affair, lined with peritoneum and completely filled with omentum. The hernia emerged through a small opening in the old mid-line scar, half way between the umbilicus and the symphysis pubis. It bulged out in a spherical pouch beneath the subcutaneous fat, forming the small tumor which could be felt before opening the abdomen. From this pouch, three long, finger-like processes extended, which lay anterior to the anterior sheath of the rectus muscle and the aponeurosis of the external oblique muscle, and underneath the subcutaneous fat. The upper one burrowed to the right in a horizontal direction almost to the anterior superior spine of the ileum. The middle one extended obliquely to the right to Poupart's ligament, and the lower one reached down vertically in the mid-line almost to the symphysis pubis. None of



these finger-like processes could be felt from the outside, as they were flattened anteroposteriorly. They widened out considerably, however, in the other diameter and measured at the widest points from about 3 to 6 cm. The peritoneum covering the hernia was very adherent to the omentum which filled the sac and to the subcutaneous fat above it.

The pelvic viscera as seen through the wound showed that both tubes had been amputated previously. The uterus was of normal size and appearance. A double oophorectomy and a panhysterectomy were done. The hernial sac was then resected. The operation took two hours. The patient made an uneventful recovery and was discharged in good condition on January 1, 1915.

The uterus after removal appeared perfectly normal. Upon section, however, there was seen in the fundus a grayish, cauliflower mass, the size of a marble, which on examination was seen to have grown from the posterior wall of the uterus near the fundus. This growth resembled very closely a carcinoma and was thought to be a carcinoma, although the processes of the tumor were a little blunter and larger than in a typical carcinoma. There was no evidence in the gross of extension of the mass or of a metastases. There was no area of necrosis in the growth. There was in the anterior wall of the uterus a small subserous myoma about 4 cm. in diameter. Microscopical section of the tumor mass in the fundus showed it to be made up of large, spindle-shaped cells, running irregularly in parts, and in parallel strands in other parts. The cells were very uniform in size, had oval vesicular nuclei and were separated by a small amount of stroma. There were small capillaries between the cells. The pathological diagnosis was spindle-celled sarcoma of the body of the uterus. The endometrium showed a chronic endometritis and there was hypertrophy of the glands. There was considerable round-celled infiltration of the tumor mass. The mass did not appear to be invasive and there were no metastases seen.

## 2. A Case of Myoma of the Appendix. DR. G. L. STICKNEY.

Mrs. S., age 39, who had for a year previous to operation complained of symptoms of chronic appendicitis, was operated upon on January 25, 1915. At operation a small clubbed appendix was found adherent to the right tube. Both structures were removed.

The appendix measured 5 cm. in length. Its diameter for a distance of 3.5 cm. from its base was uniform, measuring 7 mm., from this point it terminated in a clubbed extremity 1.5 cm. in length and 11 mm. in diameter. On section it was found to be a circumscribed solid tumor, in which a lumen could not be demonstrated.

Histologically the clubbed extremity was composed of five small circumscribed myomata, the largest measuring 3.5 mm. in diameter one situated on either side of the lumen, and three placed about the periphery.

The tumors were composed of nonstriated muscle fibers. Surrounding them generally was a loose connective tissue capsule, which in places was absent. Here the interlacing between the muscle fibers of the appendix wall and those of the tumor was so indeterminate that it was difficult to differentiate the two.

The lumen was represented by a crescent-shaped figure compressed between two myomata, which had become obliterated except at one extremity, where it was of microscopic size, and its lining epithelium intact. The mucosa was densely infiltrated with inflammatory exudate.

The subserosa was thickened, showing fibrous-tissue proliferation and many new-formed blood vessels. This connective-tissue proliferation had extended in between the muscle fibers of the external coat and the myomata. A review of the literature revealed a total of 647 cases of tumor of the appendix, of which only three were found to be myomata.

## 3. A Case of Diffuse Adenomyoma of the Uterus, with Discrete Adenomyoma over the Left Ureter. DR. G. L. STICKNEY.

Adenomyoma of the female pelvic organs, other than that of the uterus, forms a small proportion of the total number of cases. From the specimens examined in the gynecological laboratory of this clinic, one finds a proportion of 1 to 13 in a total of 183 cases.

The following case presents a diffuse adenomyoma of the uterus with a discrete circumscribed adenomyoma over the left ureter. The patient, an unmarried woman aged 36 years, for a year previous to entrance into the hospital, had complained of a dull pain over the lower abdomen, which later was referred to the rectum, and which was accompanied with a profuse leucorrhœa.

At operation a small myomatus uterus was found. A nodule was also found in the base of the left broad ligament, simulating a ureteral calculus. After a supra-vaginal hysterectomy, the left ureter was dissected free for a distance of 2 cm., and at a point about 1 cm. from the crossing of the uterine artery there was found on its anterior surface a small tumor 1 cm. in diameter which was dissected free and removed.

The uterus, besides containing many circumscribed myomata, showed a diffuse adenomyoma.

The tumor removed from the region of the left ureter is composed of nonstriated muscle fibers, surrounding two small islands of gland structure, the glands being lined with a single layer of cylindrical epithelium, and surrounded by a cellular connective tissue, presenting a picture similar to that of the uterine mucosa.

## 4. Small Bony Mass Lying on the Posterior Surface of the Right Broad Ligament. DR. WM. NEILL, JR.

Mrs. B., age 35 years. Occupation, hairdresser. Nationality, American. Admitted into C. H. I., March 4, 1915.

*Complaint.*—Pain in lower abdomen.

*Family History.*—Negative.

*Past History.*—General health good. No serious illnesses.

*Present Illness.*—Patient dates her trouble from a miscarriage in 1905.

Duration of this pregnancy, five months. A curettage was done about a week later. Following this, from three to four years, she had considerable pain in the lower left side of her abdomen. Her menstrual periods during this time were also irregular.

Two years ago, in the fall of 1913, while driving an automobile, she was taken suddenly with a sharp cutting pain in the lower right side of her abdomen. This was so severe as to demand morphia. This lasted three days, and for several weeks afterwards she had the sensation as of a mass pushing itself through on this side. Was well after this until October, 1914. From then on she felt badly all over. Could only work three or four days a week. Suffered with headache and pains across the lower abdomen and down the thighs. General lassitude. These symptoms gradually became more marked. At her menstrual period in both January and February, 1915, she had severe cramps over the abdomen, which were accompanied by a profuse yellowish leucorrhœa. This latter complaint continued up to the time of admission.

*Examination on Admission.*—The patient is a healthy looking woman, complaining of pain in lower abdomen. Heart and lungs negative. The abdomen is full and soft. Moderate tympany all over. Quite tender on pressure in lower left quadrant. No masses or muscle rigidity made out. Further examination negative.

*Vaginal Examination.*—The outlet is firm, cervix normal. A mass about 12 cm. in diameter is felt on left side of uterus. Fundus normal size, moderately backward, and only slightly movable. On the right side a small hard mass is felt, about two inches above the cervix. This is movable.

*Rectal Examination.*—Vaginal examination was confirmed. The same hard nodule is felt on the right side and behind, near the



cervix. It is so movable that it can be delivered outside the anal orifice with two fingers in the vagina and one in rectum.

Temperature and pulse normal. Urine negative. No leucocytosis.

*Operation.*—March 6, 1915. On the left side of the uterus, a tubo-ovarian cyst about 10 cm. in diameter was encountered. This was removed with great difficulty, owing to the density of adhesions. On the right side, all that remained of the tube was a stump about 2 cm. long. This was completely imbedded in the broad ligament. There was no trace of any ovary. It looked just as if both tube and ovary had been removed at a previous operation. There were no adhesions. There had evidently been a spontaneous amputation of both the ovary and tube.

Slightly below the point where the ovary should have been was a flat triangular plaque about 2.5 cm. on each side and about 1 cm. thick. This was very hard and proved to be the mass that could be pushed out through the rectum when the patient was examined under ether. It was covered by adhesions, but it was possible to shell it out without producing hemorrhage. In fact, it was shelled out without a suture or ligature being applied.

Sections from this tissue were found to consist entirely of new-formed bone. No trace of ovarian tissue was demonstrable.

*Origin.*—Of course the most natural conclusion would be that the bone originated from the ovary, which had been spontaneously amputated with its corresponding tube. This explanation is the most plausible one. On the other hand we have no evidence of any ovarian tissue from this side and it is difficult to explain the presence of such normal looking bone when all vestige of ovarian tissue has disappeared. As a matter of fact, we cannot explain, satisfactorily, the presence of this bone, which was so firmly attached to the posterior surface of the broad ligament just 2 to 3 cm. below the site of the normal right ovary.

##### 5. An Interesting Case of Tuberculosis of the Ileum from a Diagnostic Standpoint. DR. WM. NEILL, JR.

Miss H., age 17 years. Nationality, American. Admitted September 25, 1914, into the C. H. I. Surgical No. 11731. Discharged December 3, 1914.

*Complaint.*—Pain in right side of abdomen.

*Family History.*—Negative.

*Past History.*—General health good, prior to present illness.

*Present Illness.*—Beginning in the spring of 1912, patient has had a constant diarrhoea. From three to four liquid stools a day. No nausea or vomiting or abdominal pain. Never noticed any blood or mucus in stools. In February, 1914, she had an attack of abdominal colic, with nausea and vomiting. Had similar attacks during the following March and May. In August, 1914, she began having indefinite pain in the epigastrium. This lasted a week or ten days, then gradually extended downwards and localized itself in the lower right quadrant of the abdomen. This pain was a constant, dull ache, which at times became severe and caused nausea and vomiting, which seemed to relieve it. Has gotten weaker and lost all appetite. Has seen several physicians and at no time has a definite diagnosis been made.

The diarrhoea has continued. Has been running a slight elevation of temperature for the past two months. Has lost about 16 pounds in weight.

*Present Examination.*—Fairly well nourished girl slightly anæmic. Chest negative. There is a slight abdominal fullness in the lower right quadrant. A definite mass can be felt here, measuring 5 x 10 cm., indefinite in outline and lying close to pelvis. Quite painful. Rt. rectus muscle held rigid. The mass is firm and percussion note over it is dull. Not movable. Not adherent to the skin. On rectal examination, there is thickening on right side. Pelvic organs negative.

Urine negative. W. b. c. 19150. Hb. 55 per cent. Stools contain trace of blood. No mucus, parasites, or ova. Wassermann negative. Temperature 101°.

*Operation.*—September 26, 1914. A McBurney incision was made over the mass. As soon as the skin was incised, the tissues were found indurated, and this became more marked as the layers were divided. On reaching the peritoneum, it was found to be adherent to a large mass about 12 cm. in diameter. Dissection was carried on extra-peritoneally and a pocket of thick, yellowish pus evacuated, about 30 cc. The operation ceased here, as the tissues were so indurated it was not possible to separate them. A small piece of tissue was removed, which on section, proved to be only chronic inflammatory tissue. Drains were placed down to the abscess and a diagnosis of appendiceal abscess made.

The patient drained profusely and a fecal fistula developed several days later. Bismuth paste was tried without success. On leaving the hospital December 3, 1915, she had improved in health and strength. Appetite had returned, and her bowels were now regular. The mass had disappeared. She returned to the hospital regularly for dressings and all this time continued to have a fecal discharge from the fistula. It was hoped that the fistula would close itself, for it was realized that a second operation to close it would mean an extensive and dangerous undertaking.

Patient was readmitted into the hospital January 24, 1914, for the purpose of closing the fistula, as it gave no signs of closing spontaneously.

On examination, patient was much improved in health. The fistula remains open and drains freely. Bowels are regular and contain no blood or mucus.

The second operation was performed by Dr. Cullen, January 25, 1915. The fistula was closed and placed outside of the operative field. A rt. rectus incision was made. Dense adhesions had to be freed everywhere before the cæcum and ileum could be loosened. Much to the surprise of everyone, the appendix was found intact. It was thickened throughout its length but at no point did it show any evidence of ulceration. It was removed.

A hole, about 1 cm. in diameter, was found in the small bowel about 2 inches from its junction to the cæcum. This connected with the fistulous tract. On attempting to close this perforation, the tissue was found to be so thickened, that had it been possible to close it, in all probability intestinal obstruction would have resulted. The bowel was markedly thickened for a distance of about 8 inches upwards. A resection of this portion was thought advisable, as it was so badly diseased and also in view of the fact that the perforation could not be closed with any degree of safety. This was done. The two ends of the remaining bowel turned in and a lateral anastomosis performed between the last portion of the ileum and cæcum. The fistulous tract excised and a drain placed down through this opening to the cæcum. The rt. rectus incision closed without draining.

The excised portion of gut was markedly thickened, but nothing else noteworthy could be determined. A diagnosis of perforated typhoid ulcer was made, with a question mark. Sections of this tissue showed tuberculosis.

The patient has made an uneventful recovery, with the exception of small superficial abscesses forming in the old McBurney incision at various intervals. Both incisions to date are healed firmly and the patient is in excellent health.

##### 6. An Interesting Case of Appendicitis. DR. T. STARR.

Surgical No. 12820. Mrs. K. H., age 45 years. Admitted to the Church Home and Infirmary, April 30, 1915, complaining of a mass in the right groin.

*Past History.*—Negative, except for the following facts:

Patient has had a hernia since girlhood. At first, it was very soft, and easily reducible. She suffered from a constant, dull



sensation in right groin when standing, some pain when walking, but this discomfort was relieved by wearing a support.

About 14 years ago, she was taken with most intense pain across the lower abdomen. Pains were cramplike in character and gradually became localized over lower right abdominal quadrant. She was nauseated and vomited frequently.

The hernia, and the area surrounding it over a surface about the size of palm of hand, became very sensitive to touch. She had several distinct chills and probably had fever. Bowels were constipated. After a few days, the pains subsided but the hernial area remained very sensitive for about three weeks.

After recovery, patient noticed that she had more difficulty in reducing hernia than formerly and was unable to reduce the entire swelling. For the past nine years, it has been irreducible.

Since this attack, she has been able to do her usual work, but has not felt well. Appetite has been poor and she has suffered much with indigestion and constipation. For a year she suffered every evening with nausea and vomiting, but has had no such symptoms during past two years. Five weeks before admission, following considerable exercise, patient noticed that the hernia was more sensitive to pressure than usual and that stooping forward caused much pain in this region.

The next day, she had an attack similar to illness 14 years before. She suffered first with very severe abdominal cramps, general in distribution. These gradually became localized over the hernia and the immediately adjacent areas. Pain was so severe that numerous injections of morphia were required. Pressure over lower right abdominal quadrant was accompanied by much discomfort. She suffered from persistent diarrhoea for two weeks, but no vomiting.

After about two weeks, the pain began to subside, and on admission to the hospital she suffered only when considerable pressure was applied over hernia.

On examination, a woman past middle age, who appeared rather ill, was found. Examination of heart and lungs was negative. In the right groin, just beneath Poupart's ligament, there was a very firm tumor about the size of a hen's egg. Tumor was round or oval in shape and was movable to a limited extent in all directions. It was very superficial and appeared to be attached to the overlying skin. Tracing it upward, its size became reduced to a smaller neck and this apparently passed through femoral ring into abdominal cavity. There was no impulse on coughing nor could the size of the mass be reduced by pressure. There was no evidence of inflammatory reaction except some tenderness on pressure and this extended as far upward as the level of the umbilicus. There was no elevation of temperature.

Urinary examination was negative.

Patient was operated upon on May 1, 1915, by Dr. Cullen. A mid-line incision was made, in order to suspend the uterus. A piece of omentum, the size of a pigeon's egg, was found plugging the left inguinal ring. This was removed and amputated. Ring was closed with catgut.

It was found that the cæcum was drawn down to the right femoral ring and that the appendix passed through the ring and lay extra-abdominally, within the hernial sac. There was also a mass of omentum and fat, the size of a hen's egg, intimately surrounding the appendix. This was so adherent that it was not possible to reduce the appendix into abdomen. An incision was made over the hernia, and the sac was freed from the surrounding tissues. In order to reduce the mass, it was necessary to enlarge the ring by cutting through Poupart's ligament. The peritoneum was then split down to the ring and the hernial mass was drawn into the abdominal cavity. The cæcum was well surrounded with gauze and appendectomy was done with cautery. Poupart's ligament was repaired with kangaroo tendon. Hernial opening was closed with mattress sutures of kangaroo on liver needles. Closure without drainage.

Patient has made an uneventful recovery.

Pathological specimen is a firm, kidney-shaped mass, 6 cm. x 3 cm. x 3 cm. Its surface is somewhat nodular and is covered with peritoneum. Corresponding to the hilum of a kidney, a considerably thickened appendix with its mesentery is seen entering the mass. On section, a very much thickened and indurated hernial sac, surrounded by preperitoneal fat, is seen. The appendix is buried in the fatty tissue near the periphery.

#### 7. A Study of the Relation Between the Degree of Menstrual Reaction in the Endometrium and the Clinical Character of Menstruation. (Abstract.) DR. EMIL NOVAK.

This study is based upon a review of some 2000 clinical cases in the gynecological department of The Johns Hopkins Hospital. From these were selected all those in which the endometrium had been removed, either by curettage or by hysterectomy. The number of these was 339. By eliminating a number which for one reason or another were not suited for the purpose of this study, the number was reduced to 268. The entire number of cases was now easily divisible into two main groups, viz. (1) those in which menstruation, whatever its other clinical variations may have been, still retained its regular periodicity; (2) those in which the menstrual rhythm had been broken, the periods recurring at irregular intervals. This study is based upon the 159 cases of the first group, the remainder being obviously unsuitable for an investigation in which the chronology of the menstrual cycle plays such an important part.

The point of departure in any modern study of the menstrual histology of the endometrium must be the epoch-making contribution of Hitschmann and Adler, published in 1908. These investigators showed clearly that the endometrium undergoes a gradual and progressive development from the end of one menstrual period to the beginning of the next, so that its appearance varies from day to day. These developmental changes are especially characterized by a progressive hypertrophy of the glands, reaching its high point just before the onset of menstruation, in the so-called premenstrual period. Less constant and less conspicuous hypertrophic changes are noted in the stroma. The study of a large number of endometriums impresses one with the marked individual differences in the degree of these hypertrophic changes, especially in the glands. Do these differences correspond to the well-known individual differences in the clinical intensity of the menstrual flow?

The study suggested by this query must be one of comparison, and the first essential is that only those endometriums may be compared which have been removed on corresponding days of the menstrual cycle. This was accomplished by dividing the entire number of cases into groups, according to the day of the menstrual cycle on which the endometrium was removed. The first day of menstruation, being the only fixed date, was designated as the first day of the cycle. Precautions were taken to obviate or at least minimize the personal factor in the investigation.

The study of this rather large series of cases indicates, first of all, the general correctness of the teaching of Hitschmann and Adler as to the cyclical histological variations in the endometrium at different periods of the menstrual cycle. An interesting relation is shown to exist between the clinical character of the menstrual flow and the degree of endometrial hypertrophy called forth by the menstrual stimulus. Speaking generally, the more profuse the menstrual flow, the more marked the local hypertrophic changes in the endometrium. The less abundant the flow, the less striking the local reaction in the endometrium. The latter must therefore be looked upon as playing an essentially passive rôle in menstruation.

An important exception to the above generalization is en-



countered in cases of antelexion of what is commonly spoken of as the congenital type. In the 33 cases of this group, hypertrophic changes are, if anything, more marked than those noted in association with other pelvic conditions, even though menstruation is frequently scanty. This would indicate that the ovary, whose activity appears to govern the degree of menstrual hyperemia and the associated endometrial hypertrophy, is not functionally deficient in such cases, as has so frequently been stated. The scanty menstruation so commonly observed in cases of this type is perhaps due to a deficiency in a local factor whose activity permits

of the passage of blood elements from the vessels toward and into the uterine cavity. Such a theory would seem to explain the spasmodic dysmenorrhea so characteristic of congenital antelexion, for the engorged mucosa, acting as an irritant to the uterine musculature, gives rise to painful spasmodic contractions of the latter, until relieved by the onset of the menstrual flow. A physiological, rather than an anatomical, deficiency in the endometrium may also in some as yet unknown way be responsible for the sterility which is frequently seen in association with congenital antelexion.

## NOTES ON NEW BOOKS.

*A Manual of Obstetrics.* By EDWARD P. DAVIS, A. M., M. D. Cloth, \$2.25. (Philadelphia: W. B. Saunders Company, 1914.)

With the large number of excellent text-books on obstetrics already available, it does not seem that this volume supplies any particular need in this branch of medicine.

It is to be regarded merely as a handbook, the various subjects taken up being considered in the briefest manner. The author almost entirely neglects the scientific aspect, and tends to assume rather too didactic an attitude when considering the various unsolved problems met with in obstetrics.

In view of the brief and perfunctory manner in which the author treats of the various abnormalities encountered in obstetrical practice, it is difficult to see that the book will prove of very great value either to the student or practitioner.

*International Clinics.* A Quarterly of Illustrated Clinical Lectures and Especially Prepared Original Articles on Treatment, Medicine, Surgery, Neurology, Pædiatrics, Obstetrics, Gynecology, Orthopædics, Pathology, Dermatology, Ophthalmology, Otology, Rhinology, Laryngology, Hygiene and other Topics of Interest to Students and Practitioners, by Leading Members of the Medical Profession throughout the World. Edited by HENRY W. CATTELL, A. M., M. D., Philadelphia, with the collaboration of ten other eminent physicians and surgeons. Vol. IV, Twenty-fourth series. Price, \$2.00. (Philadelphia and London: J. B. Lippincott & Co., 1914.)

This volume contains 29 articles of greater or less length on medicine, surgery, diagnosis and treatment, and medico-legal and miscellaneous topics. Three of them relate to radium, one to painless childbirth, another to the routine administration of ether in measured dosage, all of which just now are of vital interest to the profession.

"A Visit to the Mayo Clinic at Rochester, Minnesota" fills up 25 pages and is attractively illustrated. It gives the special methods and treatment employed in Rochester.

An article of the same general character on the "London Clinical Congress of Surgeons," recently held in London, describes some of the methods of operating in London.

Another article by Max Broedel on "Medical Illustration" gives desirable and valuable information as to the preparation of illustrations for medical and surgical papers and the instruction of the student in drawing.

*I. K. Therapy, with Special Reference to Tuberculosis.* By W. E. M. ARMSTRONG, M. D. Cloth, \$1.50 net. (New York: Paul E. Hoeber, 1914.)

This book contains a brief account of the theoretical speculations on which Spengler bases his *Immun-körper* (serum) treatment of tuberculosis, and a general outline of the methods laid down by him for controlling the treatment of patients. The experimental and clinical data supporting his theories are given in such a superficial sketchy way, that the reader is quite unable to draw any conclusions for himself as to their reliability. The book has been written evidently by an enthusiast with very little critical insight into the immunological problems involved. In view of the fact that Spengler's fantastic theories have found no corroboration on the part of other investigators of recognized ability, and since the scanty clinical observations adduced in support of the treatment are far from convincing, it would seem that there is as yet no justification whatever for attempting to bring this method of treatment into general use.

*A Course in Normal Histology.* Vols. I and II. By RUDOLF KRAUSE. Translated from the German by PHILIP J. R. SCHMAHL, M. D. (New York: Rebman Company, 1913.)

This may certainly be regarded as among the noteworthy text-books lately published.

The first volume is devoted to the technique of microscopy. It includes an explanation of the microscope, a presentation of the methods for the preparation of microscopic specimens, including injection, impregnation, staining and mounting, together with the principles of mensuration and drawing. The use of the camera lucida is described under the last sub-heading.

The text is clear and concise. Its value is augmented by admirable diagrams and illustrations which facilitate the understanding of the microscope as well as supplying the essentials of microscopic examination.

The second volume is an atlas of normal histology and may be very highly recommended as a supplement to a good text-book.

The text is divided into three general parts devoted, respectively, to the cell, the different types of animal tissues and the structure of organs. The text is illustrated with 208 colored plates which are reproductions of the original drawings in Krause's book and are, for the most part, very good.

Krause's original work is too well known to require any comment. The translation is excellent. Each volume is in itself complete and may be used to advantage independently of the other.

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## LESIONS PRODUCED BY ARSENICALS AND THEIR BEARING ON THE PROBLEM OF SPECIFIC ARSENIC THERAPY.\*

By WADE H. BROWN, M. D.

(From the Laboratories of the Rockefeller Institute for Medical Research.)

The use of arsenic in the treatment of trypanosomiasis is now of some fifty years' standing. The first therapeutic experiments of this nature were those of Livingstone in the treatment of "fly bite" or nagana during his African explorations in 1858. True, he had no knowledge of the causative agent against which his therapy was directed and it was not until many years later, when the trypanosomal nature of nagana, surra, sleeping sickness, and other diseases of a similar character had been established, that the significance of these early therapeutic efforts was grasped and definite progress towards a rational therapy of these diseases was made.

Experimental arsenic therapy had its beginning in the demonstration by Lavéran and Mesnil of the trypanocidal action of arsenic in laboratory animals. This work, published in 1902, inspired a search for specific therapeutic agents and many other lines of therapy began to be developed in consequence—notably dye therapy, and later the use of compounds of antimony. The greatest achievement, however, came from the work of Thomas on atoxyl published in 1905, followed by that of Uhlenhuth extending the field of specific arsenic ther-

apy to spirochætal infections. With the determination of the chemical constitution of atoxyl by Bertheim and Ehrlich, the foundations for the future development of specific arsenic therapy were completed. Under the leadership of Ehrlich, the achievements in this field of therapy during the last decade have indeed been most remarkable. But the end is not yet and there are many workers striving, with hope, to improve upon the results thus far obtained.

During the past several years, a small group of workers at the Rockefeller Institute, consisting of Drs. Jacobs and Heidelberger in the chemical department, and Dr. Louise Pearce and myself, have been struggling with the problem of specific chemotherapy. There are many phases of this work about which one might speak, but we have chosen that phase about which least has been said and which to our minds, at any rate, presents at once the most difficult and the most hopeful point of attack, namely, injury and its elimination.

Since the aim of all efforts to construct chemical compounds possessing specific action against agents of infection is not only to cure, but to cure with a minimum of risk and injury to the host, it is quite obvious that the attention of the experimental worker must be constantly centered upon two points—effect

\* Read before The Johns Hopkins Hospital Medical Society, May 3, 1915.



upon the host and effect upon the parasite. These two phases of drug action are our directing forces and are of equal importance. Further, they are the criteria by which we must gauge the value of each product. Intensification of the action upon the parasite and the elimination of injury to the host become, therefore, our constant aim, and I refer here in particular to that phase of injury which gains expression in the form of organic lesions. While innumerable compounds of arsenic must have been investigated from this dual aspect, it is unfortunate that so little of the details of their action upon the animal organism has found a place in the literature. True, the pathology of arsenic poisoning has been most carefully worked out and serves as a valuable guide and standard for comparison but, apart from this, as I shall attempt to show, this knowledge avails but little in the problem of chemotherapy.

With the small group of compounds that we have studied thus far—about sixty in all—it has been our plan to determine not only their toxic limits, but the essentials of their pathological action in mice, rats, guinea-pigs, rabbits, and, in some instances, dogs. The toxicity of compounds with approximately the same percentage of arsenic has varied very widely, but not more so than the variety and severity of the tissue injury they are capable of producing.

Omitting most of the well-known lesions of arsenic, some conception of the complexity of the problem presented to the experimental worker may be conveyed by a brief description of the more important types of lesions produced in a given organ by different compounds of arsenic, the preferential action exhibited by different compounds for different organs, variations of the action in different animal species, and some of the so-called accidents. From these it will not be difficult to grasp the fundamental importance of the lesions of arsenicals to the experimental worker and perhaps also to the clinician.

The pathological changes that one encounters in the heart and blood-vessels constitute a group that are of great importance. Many of these lesions are extremely difficult of demonstration either to the naked eye or with the microscope; some are of the character of degenerative processes in the heart or vessel walls, which in themselves may seem of little importance but furnish a basis for more serious lesions, such as hemorrhage or thrombosis. With some compounds, subendocardial hemorrhages, myocardial hemorrhages, and hemorrhage into the substances of valves, have been practically constant. These lesions are especially striking in the heart of the dog, to which relatively large doses of atoxyl have been administered. They are also known to be produced by such substances as salvarsan and its various modifications.

Vascular occlusion is probably far more common as the result of poisoning with arsenic or compounds of arsenic than is generally recognized. These occlusions may be produced by either thrombi, formation of which is favored by vascular injury, or by emboli resulting from coagulation of blood elements. The seriousness of the injury produced by such vascular occlusions, of course, depends largely upon their extent and location, and all such changes may be regarded, therefore,

as accidents. Many of them may be relatively harmless, whereas others, by chance involving tissue of vital importance, may lead to most serious consequences.

Turning now to the lungs, until recently we had observed no lesions of the lungs that could be regarded as both constant and characteristic of the action of any particular compound. We have, however, observed with at least five recent compounds, a characteristic type of lung injury. This injury consists of petechial hemorrhages, finely and uniformly distributed through the substances of a lung which is voluminous and pale. With some of these compounds, a lesion of identically the same character is present in the surface of the kidney, while with others the kidney lesion is slight or entirely absent. With at least two of these compounds, reduction of the dose leads to a disappearance of the lesions in the kidney and the lesions in the lungs persist as the one characteristic change produced by the compound.

The lesions of the liver have long ranked among the most important of the organic changes produced by arsenicals. For convenience, we may divide the lesions of this organ into three groups: first, the lesions of a diffuse character, showing no preference for any particular region or structure of the organ; secondly, those lesions produced by compounds manifesting preference for the central zone of the liver lobule, and thirdly, the lesions produced by compounds acting by preference upon portal structures and the peripheral zone of the lobule.

The lesions in the first group are, for the most part, degenerative in character and closely resemble the well-known changes produced by inorganic compounds of arsenic. To these, however, must be added instances of diffuse necrosis, in which the maximal action of the compound upon the liver manifests itself in a widely distributed necrosis of individual liver cells; finally, we may place here also the group of focal necroses which are quite frequent and characteristic of the action of many compounds of arsenic.

Lesions of the central zone also include degenerative processes and necroses. Fatty degeneration of the central zone of the liver lobule is quite frequent, and in some instances the most constant and striking lesion produced by certain compounds. In other instances, fatty degeneration gives place to necrosis and most of these central necroses differ in no wise from the central zone necrosis produced by a large number of chemical agents.

We have, however, one compound on our list that produces a series of lesions entirely different from any lesion-complex with which we are familiar. The action of this compound is characterized by the fact that lethal doses in the guinea-pig lead to profuse hemorrhage into the bile-ducts from which the animal may actually bleed to death. At autopsy the appearances presented are those of a nutmeg or extremely pale and pasty liver with a gall-bladder enormously distended with blood, while the kidneys are extremely pale throughout and the urinary bladder is distended with an almost water-clear urine. We have not found this lesion-complex so constant for any other animal. It has been observed but once in the rabbit, and we have failed entirely to produce it in the



dog, which may be explained by the fact that the dog occupies an anomalous position with reference to this compound, in that dogs tolerate more than twice as much of this particular arsenical than any other animal upon which we have tested it. This is, so far as we know, the only instance in which the dog tolerates more of an arsenical than other experimental animals. It is also of considerable interest that this particular compound is one very closely related to atoxyl, a substance to which the dog manifests an extreme degree of susceptibility, tolerating only 10 mg. per kilo of body weight, as against 170 mg. for the mouse or rat.

The repair that follows this type of central necrosis in the guinea-pig is also quite peculiar. The liver of the pig that has recovered from a single large dose or from repeated smaller doses of this substance is a hob-nailed liver. This hob-nailed appearance seems to result from some degree of connective-tissue increase about the central and sublobular vessels with resulting contraction in these territories. It is, however, helped out by the fact that the liver cells are extremely large and hydropic, producing the effect of a swelling in the liver parenchyma. These changes are also associated with peculiar vacuolations that are particularly numerous about the central and sublobular vessels but are also present in other portions of the lobule. These spaces are filled, for the most part, with albuminous material, though they occasionally contain cellular detritus or a few red cells. Ascites is usually present.

In contrast to this group of central lesions, there are numerous substances that affect, by preference, the structures of the portal space and the periphery of the lobule. Most of these show a common type of action. In large doses, they produce complete necrosis of all structures in the portal space with a surrounding zone of liver cells. If the dose be reduced, however, the structures which manifest the greatest degree of injury are the bile-ducts. With even a small dose, a high degree of necrosis of bile-duct epithelium results while there is only a slight degree of fatty degeneration of the peripheral liver cells. Repair of lesions of this type takes place rapidly and is manifested by numerous mitoses in the bile-duct epithelium with an outgrowth of this epithelium toward the liver tissue and by marked proliferation of the connective tissue of the portal space. From this type of injury there results, therefore, a perilobular fibrosis which apparently interferes in some measure with the normal liver functions, as these animals always manifest a high degree of jaundice and frequently a pronounced ascites. In animals that recover from the early effects, some degree of absorption of connective tissue undoubtedly occurs, but the bile-ducts in the residue of this connective tissue are usually profuse, tortuous, and markedly dilated, indicating the persistence of some degree of bile-duct obstruction.

It is interesting to note in connection with lesions of this type that the most pronounced effect of the drug is produced by the first injection and that subsequently the dosage may be increased, even above the usual lethal limits, without materially altering the effects of the initial injection. Apparently, the tissue of this injured territory, once regenerated from pre-

viously injured cells, acquires a distinct degree of tolerance, or tissue fastness, and is not easily injured by further use of the drug. It is possible, however, to increase the dose until necroses again result. When such necroses are produced, however, they no longer involve the portal tissues or peripheral zone of the lobule but are localized beyond this territory, in the mid-zone of the lobule, and we are inclined to interpret this shifting of the point of injury as further suggesting a fastness of portal and peripheral tissues.

While speaking of the subject of fastness, it is perhaps well to call attention to the reverse of this phenomenon, namely, tissue sensitization. Many of the compounds that produce these peripheral lesions are compounds that also produce some degree of focal necrosis, and we have observed with some of them that, whereas a fastness of peripheral tissues may be produced by repeated injections, after a lapse of two or three weeks, the injection of a dose that previously produced scanty, if any, focal necrosis, will result in the production of innumerable such necroses. We know of no explanation that can be offered for this enormous increase in the focal effects of such compounds except to suggest a "sensitization" to this particular phase of the drug action.

Turning now to the kidney, this is the organ about which the greatest interest in the action of arsenic has centered, and one of the recognized types of experimental nephritis is that produced by the administration of arsenic. We have, however, not a single type of the arsenic kidney, but certainly two very sharply differentiated types with innumerable variations or gradations. The classical arsenic kidney, as is well known, is one that grossly may be described as a red kidney. On section, it exudes blood and shows a diffuse reddening from the outermost edge of the cortex to the pelvis, with little, if any, preferential action manifested in any of the zones of the kidney. There are numerous compounds of arsenic, the lesions of which conform more or less to this general picture. Some of these compounds, however, produce a greater degree of necrosis of tubular epithelium, while others exhibit a preferential action as regards the vascular changes, some producing the most marked alterations in the cortex, others in the medulla and still others showing hemorrhage and congestion confined almost entirely to the boundary zone. In some of the latter group, increase in the dose of the drug causes hemorrhage and congestion to spread through the cortex, while with others the extension is in the opposite direction.

A sharp contrast to the red arsenic kidneys is shown in a group of typically and extremely pale kidneys. With this group, there may be no evidence in the gross appearance of the organ of either hemorrhage or congestion, but on the contrary the tubular epithelium is involved to a very high degree. Connecting this group of pale kidneys with the typical red kidneys, however, comes a group of pale kidneys in which hemorrhage to a greater or less degree appears in the boundary zone. For example, arsacetin produces typically pale kidneys when administered intravenously in an amount sufficient to kill a dog in 24 hours. Atoxyl, when given in as small a dose as 20 mg. per kilo of body weight, produces a distinct and narrow



line of hemorrhage in the boundary zone of an organ that is otherwise quite pale. As this dose is increased up to the lethal limits, this line of hemorrhage spreads until it involves the entire medulla, converting it into what is essentially a blood clot. The hemorrhage also shows a tendency to spread outward, but to a far less degree, and usually the outer surface with some depth of subjacent cortex is distinctly pale, while the tubular epithelium shows marked necrosis.

Before leaving this subject, it is interesting to note also that the chronic lesions produced by these compounds of arsenic are localized and characterized according to the nature and seat of the lesions of acute poisoning. For example, compounds that produce acute lesions of the boundary zone are usually characterized in chronic stages by marked proliferation of connective tissue of this zone which, of course, may lead to secondary changes in the structures, both above and below. In all these types of renal injury, a remarkable degree of uniformity in the nature and seat of the lesion produced by a particular compound has been observed. These lesions, however, are susceptible to a certain degree of modification depending upon the size of the dose, the rapidity of action of the compounds and the length of life of the animal subsequent to the administration of the drug.

Another group to which we are inclined to attribute a great deal of importance is that of the lesions of the adrenals. The actual importance to be attributed to lesions of these organs is, of course, intimately related to their functional integrity. In the second place, no notice seems to have been taken of injury to the adrenal as a result of arsenical intoxication. We have found, however, that some degree and some type of adrenal injury are among the most constant changes produced by all classes of arsenicals. We may consider the evidences of injury from the standpoint of alterations in the lipid content, structural changes in the cortex, structural changes in the medulla, and variations in the chromaffine content. All arsenicals that we have tested cause alterations in the physical character of the lipoids in the cortex of the guinea-pig. The fine droplets in which this lipid usually exists, give place to larger droplets, especially at the outer and inner edges of the waxy cortex. The lipid which is usually abundant in this zone then begins to decrease in the middle of the zone, but increases in both the zona glomerulosa and the pigmented zone of the cortex. With some arsenicals, this decrease and shifting continues until the waxy cortex may be practically free of all lipoids except at its extreme outer and inner edges; and finally, there may be no lipid in the cortex except at the outer edge of the zona fasciculata. Corresponding to these changes in the nature and distribution of the lipid we find a greater or less degree of degeneration, necrosis and disintegration of the cells of the adrenal cortex, and with some compounds hemorrhage is a prominent feature of the structural change. Regeneration of cortical cells after injury with most compounds is quite rapid, however, and numerous cells undergoing mitosis may be observed, especially in the outer half of the zona fasciculata.

In the medulla of the adrenal, the changes are equally strik-

ing; the most striking are perhaps those involving the chromaffine substance. While with some compounds of arsenic we have noted but little, if any, alteration in the chromaffine content, other compounds produce a very marked decrease in this substance. With some, the disappearance of chromaffine takes place early and quickly with rapid regeneration, while with others the early changes are but slight and it is only after some days that a distinct reduction in the chromaffine can be demonstrated. Another change observed in the medulla is of the nature of a round-celled or polyblastic infiltration, usually associated with some degree of endothelial and connective-tissue hyperplasia. The significance of this last group of changes is still uncertain, as we have observed similar changes, but of a less degree, in the medulla of animals after acute poisoning or even in controls. As I have said, injury to the adrenals seems to be common to all arsenicals, but here again it must be emphasized that the type and degree of injury vary very decidedly with different compounds and different animal species; and it has appeared to us that the measure of injury inflicted upon the adrenal by a particular arsenical was parallel with the susceptibility of a given animal species for a given compound.

The lesions described in these several organs can serve to give only a general conception of the diversity of lesions produced by different compounds of arsenic. The changes in other organs are equally varied and of just as great importance in their practical bearing, especially those of the nervous system and of the blood and blood-forming organs, the details of which cannot now be presented. One group of changes in connection with the pancreas may be cited, however, to emphasize the question of animal specificity. We have in our list of compounds a number of substances that produce widespread fat necrosis as a part of their characteristic action in mice and rats. With none of these substances, however, have we been successful in producing fat necrosis in guinea-pigs, only once in a rabbit and a few times in the dog, but in no instance was fat necrosis a constant manifestation of the drug action in any animal species except mice and rats.

So much for the lesions themselves which, undoubtedly, are of great importance in their bearing on pathological problems, but this is not the point from which we wish to consider them.

As I have previously indicated, injury is one of the standards by which we must gauge the value of our products and it is easily seen that upon this basis many compounds can be eliminated, at once, from the list of therapeutic agents, either on account of the seriousness of the injury produced by any or all doses of therapeutic quality, or because of irregularities in their action in different animal species, or of the frequency of irregularities or accidents that may follow their use in any species.

Fortunately, there are other compounds of a more hopeful character, and these require close inspection. In determining the therapeutic value of such compounds the attempt has been made to reduce this entire relationship to a numerical basis and to express the therapeutic value as the relation of the



*dosis curativa* to the *dosis tolerata* or  $\frac{C}{T}$ . In actual practice, such expressions are of but little value and are quite misleading, as neither of these values represents constants nor anything approaching a constant in most cases. Strictly, the *dosis tolerata* has been defined as the dose that evokes neither lesions nor symptoms, but in practice this standard has not been rigidly adhered to and the values usually given are hardly more than survival doses. In truth, it is doubtful if there is, as yet, a single compound of arsenic, possessing a *dosis curativa* against experimental trypanosomiasis that produces neither symptoms nor lesions.

Further, such a basis of valuation implies a limitation of therapeutic standards to the efficacy of single dosage, or the method of *therapeia magna sterilisans*, and we are by no means prepared to concede that this is the only system of therapy or even the method of choice in all cases. The point of vital importance in determining the therapeutic value of arsenicals is the degree of injury that may follow curative applications of a given compound by whatever system it may be necessary to employ such a compound.

In weighing the pathological data, therefore, it is necessary to grasp clearly the relation between the method of employing the drug and the resultant injury, the difference between the characteristic lesions and the accidental lesions and the limitations fixed by these to the manner in which a given drug may be used. For example, there are compounds of arsenic which may be used in the theoretically curative dose with but slight recognizable injury. The usefulness of some of these compounds, however, is decidedly limited by the fact that repetition of even smaller doses may be attended by a pronounced accentuation of the injury, and in some instances an apparent sensitization occurs, giving rise to an increase in the frequency of accidental lesions produced by such compounds. On the other hand, some arsenicals permit of frequent repetition and even an eventful increase in the dose above the usual lethal limits with little, if any, increase in the injury produced by a single large dose. Instead of a dominant sensitization, we have here a rapidly developing tolerance or tissue fastness which tends to broaden the scope of usefulness of such compounds. Judged by the criterion of injury, therefore, the compounds of choice are those that manifest the most constant toxic action in all species of animals and permit of the greatest latitude of usage with a minimum of injury.

Since, from a constructive standpoint, the elimination of injury to the host is of prime importance, it follows, from what has gone before, that we must distinguish between toxicity and tissue injury, because it now appears that one may be diminished without necessarily reducing the other. It seems, indeed, that each compound of arsenic is capable of setting up a lesion-complex which is definite, although more than one compound may produce nearly identical lesion-complexes; in the complexes, moreover, the lesions of one or possibly two organs are dominant. This being true, it follows that the lesion-complex is measurably related to the chemical constitution of the compound, from which fact it follows further that

the determination and study of the lesion-complexes must inevitably influence the construction of therapeutically active drugs. But our present knowledge of how to remove the defects of chemical compounds is limited in the extreme. The outlook is hopeful, however, that as clinical and experimental experiences increase in number and precision, a rational basis of procedure may emerge.

In conclusion, in presenting this seemingly unpopular phase of specific arsenic therapy, the subject has been considered entirely from the view-point of the experimental worker. The achievements in this field of work have been truly marvelous and we must emphasize the fact that we do not wish to detract, in any way, from the value of these achievements to clinical medicine nor to create any unfavorable impression against arsenic therapy. On the contrary, we wish merely to emphasize the importance of a thorough knowledge of the lesions produced by compounds of arsenic in all their bearings as a means to an end, namely—the successful prosecution of the problem of specific arsenic therapy.

#### DISCUSSION.

DR. WELCH: I have been extremely interested in Dr. Brown's studies. They illustrate the opening up of a very broad and new field for exploration by studies in chemotherapy. He has given us a sketch of the history and I do think that Ehrlich is the one who grasped the full, broad significance of this line of investigation, partly by his insistence on the conception of the specific action of these chemical compounds upon definite tissues. One could not have foreseen, any more than he could from his early studies in immunity, where it was all going to lead us. No one could have predicted from the early studies in immunity what a vast territory was being opened up, a territory of the broadest interest, some practical and some of wide biological significance—a fascinating field of study, with its own literature and special workers who have made it their life work. Now, here in chemotherapy we have opened up another great territory with interests far beyond anything that could have been conceived.

Dr. Brown has told us about only one side of the very interesting and elaborate studies going on in the Rockefeller Institute in this direction. The ultimate aim of course is to see if improvement cannot be made in the chemical remedies. Dr. Brown has pointed out the most extraordinary lesions, some of which have perhaps no analogy at all in human pathology. It has really been demonstrated that some of these new synthetic chemical substances place in our hands the means of studying certain problems in general pathology in the most fascinating way. Some time ago Ehrlich handed me a drug, without telling me of what it was composed, which injected in small quantities into the tail vein of a mouse (an operation requiring a little skill) produces the most amazing anasarca. Just think of having a substance which injected into the circulation will produce this anasarca. I gave the drug to Dr. Evans, who repeated and confirmed Ehrlich's results.

I think Dr. Brown has gotten some organic substance, which so far as I can judge from the pictures, produces quite interesting lesions—lesions with which we are unfamiliar in human pathology. It also seems to be something which produces genuine cirrhosis, a condition which more closely resembles human cirrhosis than anything I have seen.

The whole field of experimental nephritis is one that has been most actively studied of late years. Dr. Pearce and his colleagues, Dr. Ople and others, all started with the idea that you could produce by certain drugs and poisons lesions of the kidney, which



in one instance were exclusively tubular, in another exclusively vascular or exclusively interstitial. In human beings it never seems to be safe to infer that you have exclusive tubular or other lesions. Arsenic is ranked among the poisons that belong to the vascular group, whereas uranium, the chromates, and others, produce necrosis of the cells. Dr. Brown has evidently gotten some arsenical compounds which produce mainly the predominance of tubular lesions, quite unlike the nephritis which has hitherto been attributed to arsenic.

In this field of chemotherapy, the study cannot be made quite so simple as the distinction between *dosis curativa* and *dosis tolerata*. Although Dr. Brown did not elaborate the fact, it must be patent to everyone that very severe toxic lesions are produced by certain doses, for it is a familiar fact that one and the same substance given in minute or small quantities may be an admirable stimulant or curative, and at the same time act as a very severe poison in other doses. I do not think this necessitates very depressing views as to the possibilities of arsenic therapy. It is very interesting to know of these lesions.

I wonder if Dr. Janeway may not be able to give us, from the human side, his experience as to the toxic effect of some of these arsenical compounds.

DR. JANEWAY: It has been a very great pleasure to me to see the demonstrations of Dr. Brown's specimens. I had known of the work but had not had an opportunity to see the actual lesions. These things have a very important bearing which is being borne in on us more and more every day as we meet with unexpected toxic effects of salvarsan. We have this winter seen quite enough to convince us of the desirability of knowing the types of lesion which salvarsan may produce. In particular, many of you who have been present at the Saturday clinics may remember the Hindu, who as the result of an apparently safe dose of salvarsan, developed the most intense renal lesion, with blood in the urine, marked oliguria, oedema and in addition jaundice with a swollen liver, which still persisted when he left the hospital in fair convalescence at the end of nearly two months. At one time I feared he was going to have acute yellow atrophy of the liver. He evidently had extensive necrosis within the liver, possibly the type of lesion which Dr. Brown has shown in the portal spaces. That seems quite a possibility. Our renal lesions have been more frequent than hepatic lesions. Renal lesions plus general reactions have been our greatest bug-bear in the use of salvarsan therapy.

I have wondered to what extent the hemorrhages Dr. Brown obtained were really a specific manifestation of the drug. I once saw a case which made me feel that possibly it was not only the nature of the irritant which determined renal hemorrhage. We had a young woman in the City Hospital, who had a subacute nephritis, whose only discoverable cause was the existence of an active syphilis. At autopsy, she had on one side a perfect example of the large white kidney, with extensive degenerative tubular lesions; on the other side a perfect example of the hemorrhagic type of nephritis. The kidney actually dripped blood and was a mass of hemorrhages. The different lesions in the two kidneys in this patient were apparently due to the same circulating poison.

DR. ROWNTREE: Having at one time worked in the fields of chemotherapy, Dr. Brown's work has been peculiarly interesting to me. It pleased me a great deal to hear him give Thomas so much credit for outlining the fundamental principles of chemotherapy.

The introduction of salvarsan, Ehrlich's greatest achievement in this field, is usually accredited to the fact that he forsook the pentavalent and worked with the trivalent form of arsenic. In view of the almost infinitely greater trypanocidal value of the latter, it is peculiar to find that there is no corresponding striking difference in the pathological lesions produced by the two forms.

Dr. Brown demonstrates a tissue specificity in response to drugs. Other forms of specificity impress the worker in these lines. Trypanosomes of various strains will all be killed by certain antimonials; whereas spirochetes, which are biologically closely allied, under the same conditions will not be affected at all. Several points come under consideration; specificity of the infecting organism, specificity of tissues and specificity of species. The marked variation in the pathological picture in different species may in part explain the variation of tolerance in different species and the variation in the lethal dose of a drug.

Some years ago Dr. Abel and I studied the effect of some anti-mony preparations on trypanomiasis in various laboratory animals. We found it was possible to get an active trypanocidal agent which could be given repeatedly in large doses without any apparent injury to the host. It was easier, however, to obtain results in small animals, such as rats and mice.

DR. WADE H. BROWN: In reply to Dr. Rowntree, these lesions were all from pure toxicity experiments—no infection existed. Mention was made of differences in toxicity in different animal species. In some instances these differences were very striking and they are important in connection with the great differences that prevail in the system of testing the trypanocidal action of drugs in different laboratories. For example, the Germans rely mainly on mice, the English lay stress on the use of rats, while the French have used a greater variety of animals, mice, rats and guinea-pigs. Thus, many difficulties arise in the interpretation of results. Some think that the results with mice mean very little and that those from rats are much more important, while still others lay greater stress on the results obtained in guinea-pigs. I think, as a matter of fact, that none of these views are wholly correct. I do not believe there is any one species which tells the story. I think the only rational procedure is to use several species and large series of animals. As it happens, we have had our best curative results with the guinea-pig—an animal with which others have not been able to obtain their best results. Our results may be referable to the better tolerance of guinea-pigs for the arsenicals we have used.

As to the question Dr. Welch asked in regard to the specificity of any of these compounds for the vascular system or the tubular epithelium of the kidney, I do not believe we have as yet any arsenical that we can say is specific for one tissue or the other. As a matter of fact, there is always a combined action, but vascular injury of some description is far more common than epithelial injury.

I tried at the conclusion of my paper to emphasize the fact that this presentation was from the standpoint of some of the difficulties that the experimental worker has to contend with. I think there is nothing anywhere that should be interpreted as disadvantageous to the practice of specific arsenic therapy. There are some facts, however, we should know as clinicians as well as experimental workers. The effects described are the exaggerated effects brought out in the host by toxic doses. In many instances the therapeutic dose is far below these doses and produces very little injury, as far as we can determine.

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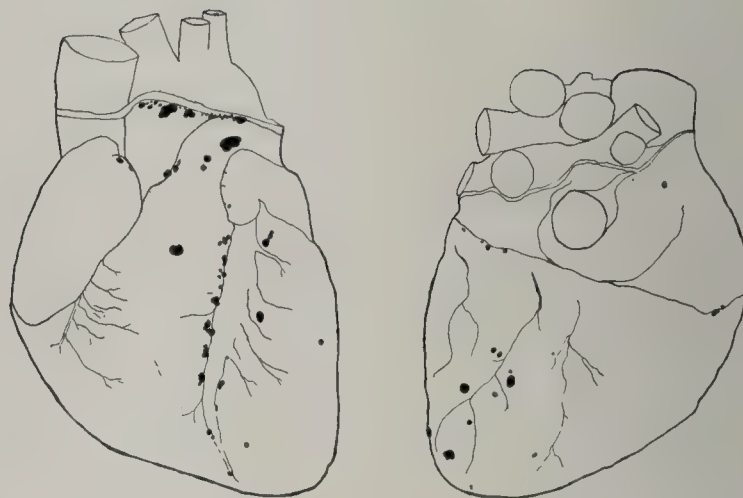








FIG. 1.—Large lymph-glands: (a) About the base of the heart and great vessels from which retrograde infection of the epicardial lymph-channels took place. (b) Minute blastomycotic nodules along the perivascular lymph-channels.



FIGS. 2 and 3.—Illustrating the distribution and relative size of the minute focal lesions along the course of the lymph-channels. Fig. 2, the front; Fig. 3, the back of the heart.

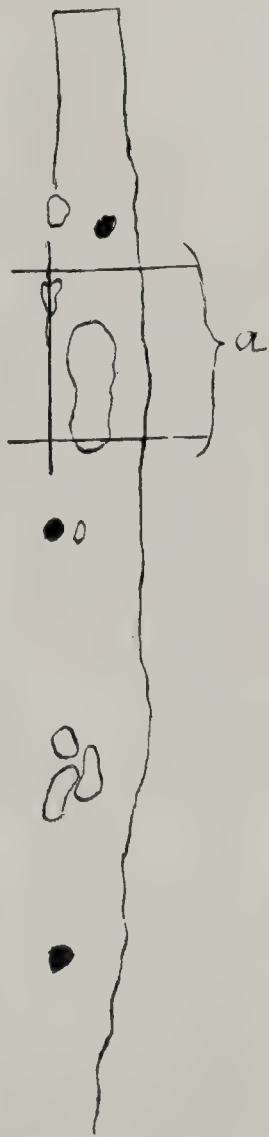


FIG. 4.—Miliary subepicardial blastomycosis. Photomicrograph, 35 diameters. In the chart to the right, the region *a* is that shown in Fig. 5. The lymph-channels crowded with blastomycetes are outlined empty; the blood-vessels are shaded solidly black. In the photomicrograph they look alike.

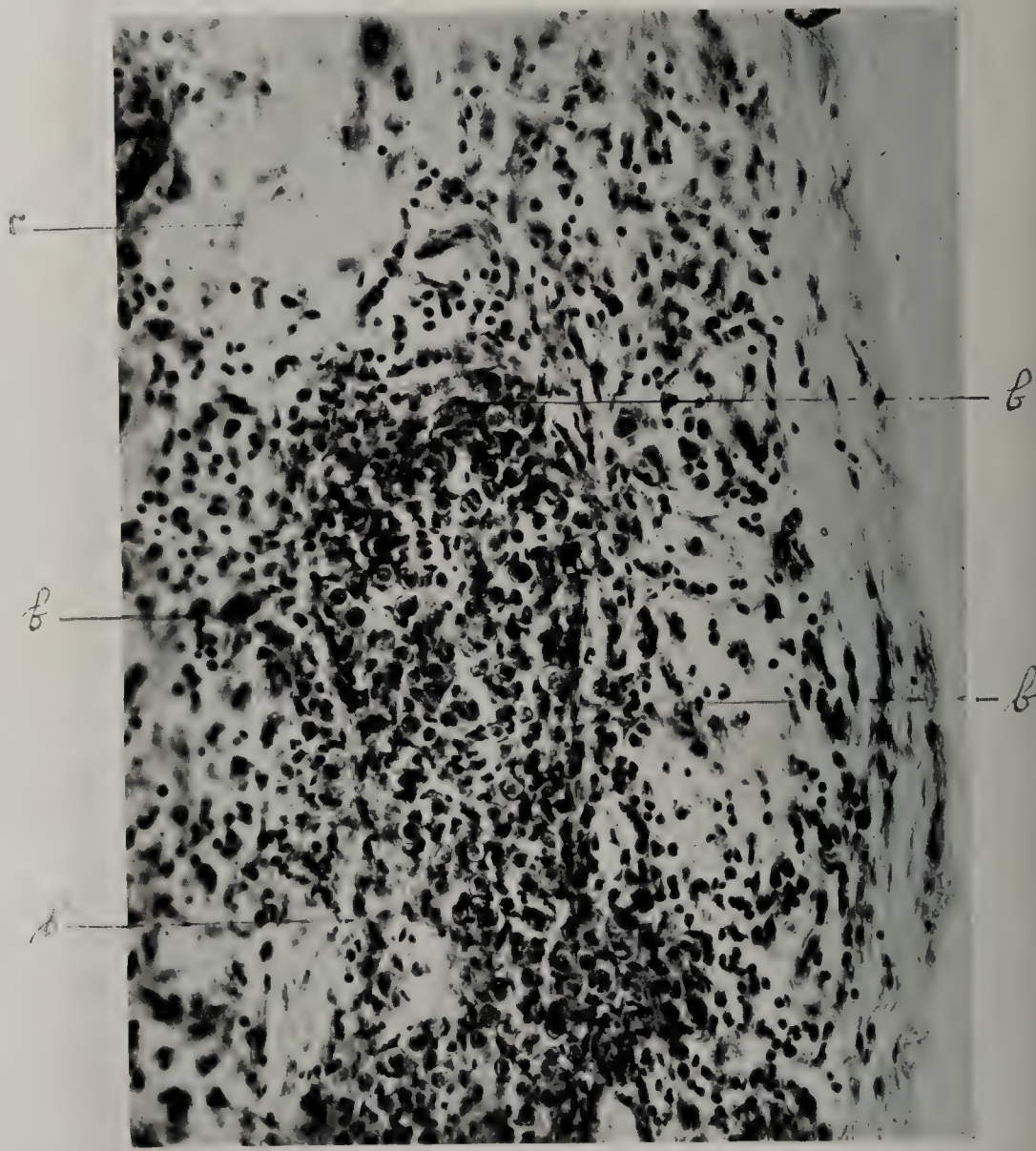


FIG. 5.—The large lymph channels containing many blastomycetes shown in the area (a) of chart to Fig. 3. In this Fig. 5, the lines (b) are drawn to the edges of this lymph channel. (c) Subepicardial adipose tissue. ( $\times 275$ .)



# MILIARY BLASTOMYCOTIC RETROGRESSIVE LYMPHANGITIS OF THE EPICARDIUM.<sup>1</sup>

By E. R. LECOUNT.

(From the Pathological Laboratory of Rush Medical College.)

In most of the summaries in medical literature of the various contributions to our knowledge of systemic or generalized blastomycosis, comparisons have been made between this disease and coccidioidal granuloma, which it greatly resembles, and attention has been especially directed to the greater frequency with which the lymphatics, both glands and channels, are involved in the latter disease.<sup>2</sup> With greater opportunity to examine conditions in systemic blastomycosis, it has been learned that infection of the lymph-glands is by no means rare, although the disease is disseminated throughout the body by the blood; also that the changes in the lymph-glands are definite, grossly evident and closely resemble those caused by tuberculosis.<sup>3</sup> Stober and the writer have repeatedly found the lymph-glands involved in regions adjacent to extensive blastomycosis. Stober says: "A general enlargement of the lymph-glands was found at necropsy in about one-third of the cases (29), and blastomycotic lesions, in addition to having been found in the peribronchial lymph-nodes a number of times, were on two occasions in this series also found in the submaxillary, axillary and inguinal glands."<sup>4</sup>

Bassoe<sup>5</sup> found changes in the mesenteric and retroperitoneal lymph-glands characteristic of blastomycosis, associated with extensive amyloid degeneration, but without fungi.

That the similarity to tuberculosis extends even to the occurrence of retrograde dissemination along lymph-channels is illustrated by the following observation:

In 1911 a Bulgarian laborer, age 25, entered the Cook County Hospital to the service of Dr. Amerson with a cellulitis of the left arm which yielded to boric acid fomentations and to external applications of iodine and ichthyol. The cellulitis was of two months' standing; there was a sharply localized swelling just below the cubital fossa on the front of the arm and on the wrist a healing abrasion; there was no lymphangitis demonstrable connecting these two lesions. The man remained in the hospital eight days and was discharged much improved and at his own request.

<sup>1</sup> Reported at the 13th annual meeting of the American Association of Pathologists and Bacteriologists in Washington, May 6, 1913.

<sup>2</sup> See for example, S. Hektoen, "Systemic Blastomycosis and Coccidioidal Granuloma." *Journ. Am. Med. Assn.*, 1907, XLIX, 1071-1077.

<sup>3</sup> See descriptions and illustrations in "Systemic Blastomycosis." E. R. LeCount and J. Myers: *Journ. Infect. Dis.*, 1907, IV, 187-200.

<sup>4</sup> Systemic Blastomycosis. A report of its pathological, bacteriological and clinical features. *Arch. of Int. Med.*, 1914, XIII, 545.

<sup>5</sup> P. Bassoe: Disseminated Blastomycosis. Report of a case involving the lungs, lumbar vertebræ and subcutaneous tissue, with multiple abscesses and fistulæ and extensive amyloid degeneration. *Journ. Infect. Dis.*, 1906, III, 97.

A year later, a Bulgarian laborer, 26 years old, with the same name, entered the same institution to the service of Dr. Ormsby. He had been sick for three months with a cough, fever and multiple abscesses and ulcers on the body, which were quite promptly recognized as blastomycotic; and in the pus of one of them the organisms were found. He walked or was helped by a friend into the hospital, but died two hours after entrance.

Both of these Bulgarians talked very brokenly and accounts of their illness were obtained with difficulty. Up to the present time attempts to learn more regarding them have been fruitless, notwithstanding the kind help of Dr. Dosu Doseff, one of the Chicago Bulgarian physicians. From the correspondence in name and age, however, it is to be assumed that the two persons were in reality the same individual. From the post-mortem examination made 16 hours after death, the following data were obtained.

*Anatomic Diagnosis.*—Miliary, submiliary and nodular blastomycosis of the lungs; miliary and nodular blastomycosis of the tracheo-bronchial and mediastinal lymph-glands with abscess formation; multiple blastomycotic ulcers of the skin; healing and unruptured subcutaneous abscesses; nodular blastomycosis of the spleen and kidneys; miliary blastomycosis of the pericardium and peritoneum; blastomycotic abscess of the pancreas; marked emaciation and anæmia; small decubital necrosis over the sacrum; fibrous (left) pleuritis; hyperplasia of the axillary retroperitoneal and mesenteric lymph-glands; fibrous adhesions between the colon and under surface of the liver, between the transverse colon and the posterior surface of the stomach; stellate white scar in the meso-sigmoid; ossified costal cartilages.

Some idea of the extent of the disease may be obtained from the following account of the external appearances:

There are on the body (1) numerous regions in which there are unbroken abscess cavities, soft and fluctuating; (2) other regions where the skin over these has necrosed regions, round, elevated and containing soft necrotic material, and (3) regions which are similar to the last mentioned, but which are healing, covered with thick dark reddish-brown crusts.

These various lesions vary in size from a millet-seed to 4 or 5 cm. in diameter and are found as follows: on the forehead, about the external occipital protuberance in the scalp tissues, in the skin of the neck; about 12 on the face; a large lesion about the right nipple; many small ones over the front of the chest and over both arms; on the left hand at the base of the thumb and over the outside of the left wrist one each; numerous small ones on the back; one opposite Scarpa's triangle of the right thigh; small lesions on the front and back of each leg; large ones in the skin of the front of the right thigh, the inner surface of the left foot, and behind the ankle.

The left hand and foot are encased in surgical dressings and under another dressing there is a region 6 cm. long and 2.5 cm.



wide, on the outside of the lower third of the left leg, where the skin is absent, exposing gray necrotic subcutaneous tissues. The border of this place is rough and irregular, soft, easily torn and bluish-red. Fourteen lesions are more than 1 cm. across; altogether they number 110.

When a careful examination was made of the heart, conditions of unusual interest were found, reminding us again that any post-mortem examination of the body of a person dying from systemic blastomycosis may reveal changes new to pathological anatomy.

The heart has about 100 lesions easily seen by gross examination of its external surface.<sup>6</sup> Their distribution along the course of the blood vessels, especially the anterior coronary vessels, is shown in Figs. 1 and 3. They vary from 0.5 to 6.5 mm. About half of them are from 2 to 6.5 mm. in diameter, the largest 4 by 6.5 mm. They are firm, pinkish-brown, generally paler than the adjacent muscle, and round, oval or irregular from coalescence. Most of the lesions are elevated 1 mm. or less; about a dozen and including some of all sizes are slightly, if at all, elevated.

The involvement of the lymph-glands about the bifurcation of the trachea and root of the aorta (Fig. 1) is marked, even greater than I have described in another place with Myers.<sup>7</sup>

<sup>6</sup> I am pleased to acknowledge my indebtedness to the great care taken by Dr. Mary Mitchell in charting the lesions for Figs. 2 and 3.

<sup>7</sup> L. c.

The changes in them are similar with a striking resemblance to tuberculosis in both the gross and microscopic alterations.

The blastomycetes were recovered in pure culture without any trouble from the pus in an unbroken subcutaneous abscess removed at the post-mortem examination.

*Microscopic Examination.*—In a number of the epicardial lesions the conditions are quite similar. They stretch along the outside of the heart in the deeper parts of the epicardium in their beginnings and have their origin in an extension of the disease along the lymph-channels.

Only the very superficial parts of the myocardium are involved. The nodule illustrated in Fig. 4 is a little over 2 mm. long in the section photographed for this illustration and 0.2 to 0.5 mm. wide in the various sections examined of the series through it. As the peripheries of the lesions are approached in studying them, the blastomycetes, which are very abundant, become limited to small lymph-channels; when traced back again into sections where the most marked changes are present, these lymph-channels become increasingly difficult to follow (Fig. 5). In such sections the lymph-channels usually occupy the centers of the lesions. These lymph-channels contain no red blood corpuscles in any of the sections. The necrosis in these minute blastomycotic abscesses is slight, the cellular exudate being largely formed by mononuclear cells.

## AN OCCASIONAL FEATURE IN THE PATHOLOGY OF SPLENOMEGALY.

By THOMAS P. SPRUNT, M. D.

The lesion which forms the basis of this note has been described in the spleens from cases of Banti's disease or similar conditions by Marini<sup>1</sup> (1902), Stengel<sup>2</sup> (1904), Simonds<sup>3</sup> (1908), and by myself<sup>4</sup> (1911). Somewhat similar appearances are only very briefly mentioned by Hamill<sup>5</sup> (1902), and by Borissowa<sup>6</sup> (1903). Kockel<sup>7</sup> and Bittroff<sup>8</sup> have described analogous processes in the lungs in chronic passive congestion and in pernicious anæmia.

Microchemical studies<sup>4</sup> have shown that we have to do with a selective impregnation of elastic tissue with the phosphates of calcium and iron, giving rise to ochre-colored patches about as large as grains of wheat and easily visible to the naked eye on incising the spleen. They have a characteristic microscopic appearance with moderate magnification, best indicated by the accompanying illustrations (Figs. 1 and 2).

My interest was again aroused in this connection by the occurrence of another case which showed this peculiar feature, and by the report of Gibson<sup>9</sup> who describes in several spleens from different diseased conditions what is evidently the same lesion, and attributes to it etiological importance, considering these areas agglutinated masses of organisms of the nature of a streptothrix. His description and particularly the illustrations which accompany his paper leave no doubt that we are dealing with the same pathological process. His opinion was based solely upon morphological evidence and

strengthened by certain staining reactions; but in spite of this insufficient evidence, it has excited a considerable degree of interest in a few workers in this clinic, has been mentioned editorially by journals<sup>10</sup> in this country, and is quoted in a recent article by Bunting and Yates<sup>11</sup> as evidence in favor of the infectious nature of splenic anæmia.

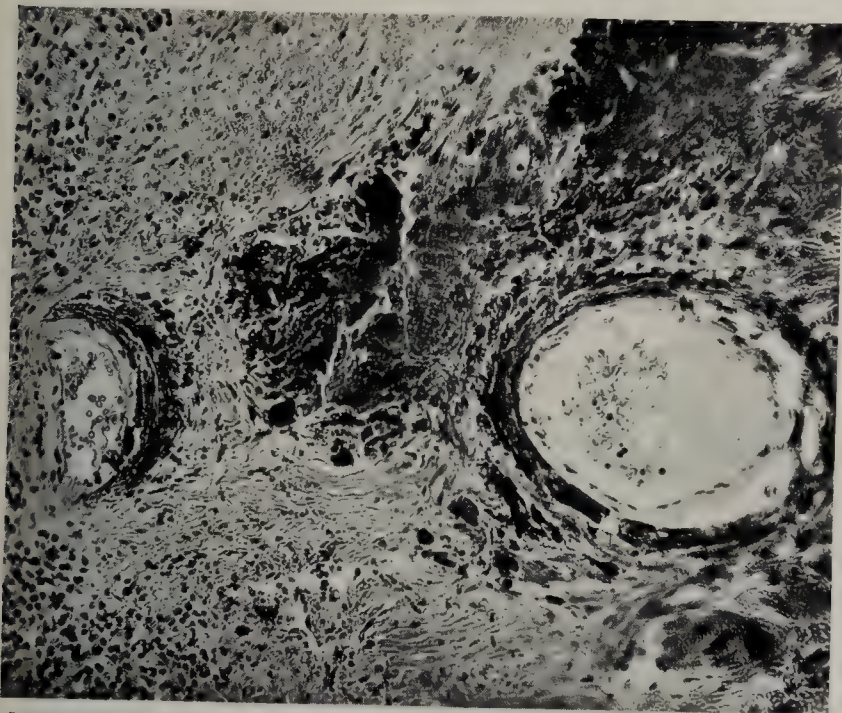
Several forms of splenomegaly are undoubtedly of infectious origin, notably the tuberculous, the syphilitic, and those occurring in chronic streptococcus infections. Recent work<sup>12</sup> indicates that the leukæmias are probably of an infectious nature. Perhaps in the future it may be demonstrated that the more obscure forms of splenic enlargement, such as the group comprising the splenic anæmias and Banti's disease, belong in the category of infectious processes. Such a demonstration, however, must rest upon more convincing evidence than suggestive morphological appearances, which admit of more than a single interpretation. Because of the probable misinterpretation which Gibson has placed upon the lesions studied by him, it has seemed desirable to call attention again to the exact nature, morphological and chemical, of such lesions in the spleen.

The ochre-colored patches are found microscopically to consist of narrow golden or hematoxylin-staining bands arranged concentrically in the walls of small vessels having a diameter of from one-tenth to one-sixth of a millimeter and, in addition,



of broader similar bands less regularly arranged in the nearby trabeculae. Between these coarse strands, fine yellow or dark staining filaments form a delicate network which is naturally emphasized by Gibson, who was impressed by its resemblance to a fungus. The club-shaped extremities of some of these filaments, which he describes, are easily made out and such appearances may be found unassociated with the more striking coarser lesions.

All this material stains readily in the tests for iron; it is easily dissolved and disappears from the sections when treated with dilute mineral acids or stronger oxalic acid, leaving a hyaline area which stains very poorly, gives the so-called "elacin" reaction of Unna<sup>13</sup> but does not take the usual elastin stains. The most instructive preparations are made by first treating sections with potassium ferrocyanide and hydrochloric acid and then staining with orcein. By this method the iron-containing tissues are colored blue and the elastic tissue a silky brown, and such preparations show very well



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FIG. 1.—Heavy accumulation of the incrusting salts. (Hæmatoxylin and eosin.)

the apparently normal brown fibers running over into the wavy blue fibers, which still retain some of the characteristic morphology, but are continuous with the dark blue, straight, broken bands in the center of the lesions. The transition is especially well shown in the fine filamentous network, where the two stains can be seen coloring the same fiber in different parts of its course.

As already remarked, all this material is quickly removed from sections by dilute mineral acids, even by the small amount in the ordinary elastic stains (less than 1 per cent), unless the iron has first been converted into Prussian blue.

On the other hand, the several strains of streptothrix organisms which I have tested may be exposed to 10 per cent mineral acids for over an hour with little or no change in their staining reactions.

Further microchemical details may be obtained by reference to the articles already mentioned, and a comparison of the

illustrations accompanying the several papers will convince the reader of the unity of the lesions described. There is no local inflammatory reaction whatever about these structures in the spleen, although in the analogous condition in the lung, found in rare cases of chronic passive congestion, Bittrolff reports a very definite foreign-body reaction with numerous giant cells which contain fragments of the incrustated fibers.

The recent case showing this peculiarity is here briefly reported through the kindness of Prof. Finney:

The patient, a white man, from Georgia, aged 30 years, was admitted to the hospital on June 18, 1913, complaining of "splenic anæmia." He gave a fairly definite alcoholic history, and had had what may have been a chancre in 1903 without any subsequent development of secondary lesions. He suffered from a left hemiplegia for nine weeks in 1904. He dated the present illness from July, 1911, when, after an attack of "malaria" of three weeks' duration, his spleen remained large. In September, 1912, there occurred a convulsion, after which he was unconscious for thirty minutes. In November, 1912, January, 1913, and May,



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FIG. 2.—Lesion less marked. Note different stages of process in internal elastic lamella. (Hæmatoxylin and eosin.)

1913, similar attacks were experienced. In May there was also a severe attack of pain over the liver continuing four hours; and again in June one still more severe. He had taken thorough courses of quinine with no effect on the symptoms or spleen; similarly, large doses of mercury, iodides and sodium cacodylate had been without apparent effect on the size of the spleen.

Examination revealed a moderate pigmentation of the exposed parts, pyorrhœa alveolaris, a scar on the penis, a very large spleen, and an apparently small liver, flatness stopping 5 cm. above the costal margin in the mammillary line. There was no general lymphnodular enlargement and nothing to indicate a lesion of the central nervous system.

The urine was normal; the blood pressure 115 mm. Hg.; the temperature varied from 98 to 100° F., reaching the latter point twice in 12 days; the pulse rate was about normal. The Wassermann test was negative. The blood examination showed no anisocytosis nor poikilocytosis; red cells, 2,500,000; leucocytes, 1,160; hæmoglobin, 40 per cent. Differential count of leucocytes; polymorphonuclear neutrophils, 73.6 per cent; eosinophiles, 2.4 per cent; basophiles, 0.8 per cent; small mononuclears, 15.2 per cent; large mononuclears, 6.4 per cent; transitionals, 1.6 per cent.



Of tuberculin tests, the Calmette 1 per cent and 5 per cent were negative; the von Pirquet test was positive.

On June 30 splenectomy was performed by Dr. Finney. After the operation the temperature remained about 102° F., occasionally rising to 103°. A small stitch abscess developed in the wound, and there were signs of a pleural effusion on the left side with a moderate leucocytosis. After a thoracentesis (400 cc. of clear fluid) his condition gradually improved, but the patient left the hospital against advice before his temperature had become normal.

The spleen was adherent only to the tail of the pancreas. It was quite large, measuring 22 x 9 x 13 cm. The consistence was somewhat firmer than usual; on section the cut surface was dark greyish-red, fairly smooth, with widely spaced Malpighian bodies and rather prominent trabeculae, in which could be seen scattered here and there the small ochre-colored patches, 1 to 3 mm. in diameter, usually surrounded by a purplish zone. Microscopically, the spleen was the counterpart of the one already described.

The occurrence of these lesions in the spleen, removed at operation and examined immediately in the operating room, disposes effectually of Hueck's criticism that such findings are due to the post-mortem absorption of iron.

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## MICHAEL SERVETUS.

### DISCOVERER OF THE PULMONARY CIRCULATION.—HIS LIFE AND WORK.

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Estimated from the standpoint of our prevailing conceptions of evolution and heredity, the human being is to be regarded as the product of his environment. In proportion to the physical perfection of the environment, the richer its elements of geographical charm, beauty and healthfulness of climate, the more varied its range of accessible food products, in the same degree its human inhabitants should develop into a nobler type. As the high priest in Mozart's "Zauberflöte" idealizes the thought in song:

"In diesen heiligen Hallen  
Kennt man die Rache nicht  
Und ist ein Mensch gefallen  
Ruft Liebe Ihn zur Pflicht."

The human being may be assumed to develop a purer and more admirable form of physical and psychical excellence in accordance with the natural conditions that surround him. Yet the physical universe, even when revealed in its most lovely aspects, does not always tend to the ennobling and elevating of those who are constantly exposed to its power. Despite its grace of outline, the rapture that abides among its lonely hills, its misty mountain tops, the dawning sun that furrows all the orient into gold, "while every prospect pleases," man retains his original vileness:

"Die Welt ist zufrieden überall;  
Wo der Mensch nicht hinkommt mit seiner Qual."

Among the master works of the Divine Artist, the Lake of Geneva assumes a foremost place. From every point of view, geographical, historical, literary, its shores are rich in complex memories and associations, tracing back for more than 20 centuries to the time described by Julius Caesar when he met the Helvetian host at the bridge over the Rhone, and broadening through the slowly forming ages until we reach the periods forever linked with the names of Calvin, Knox, Servetus, Voltaire, Rousseau, Gibbon, Madame de Stael, Byron, Ruskin. Mt. Blanc looks down from the region of Savoy and its evening glow lights up the lake with a brilliance that neither art nor language has been able to portray. Yet it was in Geneva that there was enacted one of the most deplorable tragedies that have darkened the annals of the modern world—the death of Michael Servetus at the stake on October 27, 1553.

Apart from the sphere of the scientist and the student of theological development, the name of Michael Servetus is almost unknown to our contemporary world, and when introduced, save in the esoteric circle of the medical investigator, it is suggestive only as an echo of a vanished age. Yet no name in the long record of scientific evolution is more worthy to be rescued from the oblivion which has enveloped it and to be brought into the clear light of our modern day. Servetus may be regarded as marking one of those distinctive processes or



advances by whose agency or activity science in all her phases "slowly broadens down from precedent to precedent." The range of his acquirements seems to have embraced every form of learning in his age, accessible or available. In a measure, at least, he had realized the ideal of Francis Bacon and taken all human knowledge as his province. In the field of medicine he revealed a creative power which heralded the coming of the modern era; his skill in polemic theology was unsurpassed—subtle, acute, penetrating; and with these rare qualities of intellect, was blended the charm of a noble and generous spirit. Yet, with all these graces of heart and intellect, he became the victim of the prevailing bigotry and intolerance which characterized every form of religious thought, Catholic or Protestant, and through the resistless power of Calvin, the political, as well as the theological, autocrat of Geneva, he suffered death at the stake.

Now that the Reformed Churches of France and Switzerland have erected at Champel, the scene of his martyrdom, an expiatory monument to the memory of Servetus and the people of Vienne<sup>1</sup> have perpetuated in marble or bronze their reverence for his genius and their commiseration for the tragedy of his death, the obligation becomes more imperative than ever to reveal the truth of his history; to dispel the errors and fabulous assertions with which passion and intolerance have obscured his fame, and to exhibit in abiding clearness the record of the scientific discoverer, the harbinger of the modern world in the field of medical exploration in relation to the circulation of the blood. To accomplish this purpose, we shall freely avail ourselves of the invaluable record of the Abbé d'Artigny, Canon of the Cathedral of St. Michael's at Vienne, who had also at his disposal, during the time that he was engaged in the preparation of his *Memoirs*, the archives of the archbishopric of Vienne, then preserved in complete condition. His statements, derived from so eminent a source, will hardly be called in question by the most sceptical inquirer, or the most hostile student of the life of Servetus.

The most authentic accounts represent Servetus as having been born at Tudelle in Navarre in 1511. The date is inferred from the reply which he made to his judges at Vienne in April, 1553, declaring himself at that time to be 42 years of age. The most accurate and trustworthy biographers represent him as having been born at Villanueva-on-Aragon, as at a later period he assumed, in accordance with the usage of former ages, the name of his birth-place, calling himself Michael de Villeneuve. When at a subsequent time he was reproached by Calvin for concealing his name, he justified himself upon the ground that he had assumed the name of his native city. Yet, when arraigned in Vienne, he declares to the judges that Tudelle is his native city. The discrepancy, however, is more in appearance than in reality and can be explained upon the natural supposition that the ancestors of Servetus came originally from Villanueva and afterwards acquired a residence in Tudelle. During the age of Servetus and for centuries preceding, patronymics and local designations were used without the definite and precise significance characteristic of a later time, being

modified or varied as changes of place or condition might render desirable or expedient. As the surname did not affect the issue of the trial, some such cause as we have suggested will present a plausible reason for the change. His real name, Servetus, was one that he deemed it prudent to conceal from motives of a nature such as readers of "The Antiquary" will readily recall. During the entire judicial procedure he is addressed as Michael de Villeneuve, the title he had assumed in France. Even within a comparatively recent period Coleridge and Poe, upon entering the military service, disguised their identity by the assumption of pseudonyms.

From early childhood, Servetus displayed a rare intelligence and a marked fondness for the attainment of knowledge. So devoted was his application to study that at the age of 14 he had acquired the elements of Latin, Greek and Hebrew, also an accurate acquaintance with mathematics and the crude mechanical philosophy of the time, as well as the scholastic theology, then recognized in the universities of Europe as the embodiment and the vital essence of religious truth. The study of Holy Scripture and his mode of interpreting its teachings in reference to the Trinity was the specific cause that aroused the antagonism of Calvin and "marshalled him the way" to the stake at Champel. According to his biographers, the father of Servetus, who was by profession a notary, sent him to Toulouse in order to devote himself to the study of law. The reputation of the ancient city for sanctity had gone out into all the medieval world and the fame of its holiness was blazoned by the inscription placed over the vault which was reputed to contain the bones of seven of the twelve apostles, "Non est in toto sanctior orbe locus." More than two centuries later than the time of Servetus this hallowed center of apostolic tradition became the scene of the Calas tragedy (1762), more atrocious in spirit and more ghastly in detail, if such be conceivable, than that enacted at Geneva in October, 1553. If the testimony of Servetus himself is to be accepted as trustworthy, he did not imbibe his heretical opinions in regard to the doctrine of the Trinity during his student days at Toulouse. His inoculation with this fatal heresy may be assigned with probability to a later period and its origin traced to the influence of his sojourn in Italy, which brought him into contact with the prevailing theological tendencies of the country, notably at variance as they were with the orthodox or accepted interpretation of the mystery of the Trinity.

According to the declaration of Servetus, he entered the service of the Holy Roman Emperor, Charles V, of Germany (also King of Spain under the title of Charles I), at the age of 15 years, a circumstance which enables us to fix the year definitely as 1526, he having been born in 1511. He seems to have been associated in some capacity with the confessor of the Emperor, and was present when Charles was crowned at Bologna instead of Rome in 1530, assuming the title of King of Italy, as well as that of Emperor. That Servetus had been in Italy was known to his biographers, as he refers to it in the preface to the first edition of his "Ptolemy," but the contemporary political events with which he was associated by virtue of his relation to Charles V make it possible to fix the duration of

<sup>1</sup> Vienne in the Department Isère, France.



his residence with at least approximate accuracy. Trinitarian heresies, among the earliest to reveal themselves in the development of theological dogma, were at this time rife in the cultured circles of Italy, now prostrate under the power of Charles V. The intellectual vigor of Servetus, as well as his critical acquaintance with the scholastic philosophy and the method of disputation prevailing in the universities, assured him a conspicuous place in the polemic combats of the time, when the dawning reformation and its novel teachings were the absorbing and almost exclusive theme. Luther had confronted Charles V at Worms only a few years preceding the coming of Servetus into Italy, and the thought of the world was concentrated with eager and ever-broadening interest upon the attitude and the innovations of the Monk of Wittenberg. In accordance with the law of evolution in the sphere of theology, the accepted doctrine of the Trinity was selected as one of the vital points to be assailed and Servetus was chosen by general consent as the protagonist who was to deliver the first blow. Although a youth of 18, he had devoted himself to the preparation of his treatise, "*De Trinitatis Erroribus*," his relentless antagonist, Calvin, being at the time only 20. De Quintain or Quintana, the confessor of Charles V, being called to Germany, Servetus accompanied him, it being understood, however, that he was to maintain an intimate relation with his Italian associates through the medium of correspondence.

The following year (1531) De Quintain, the confessor, died, and Servetus found himself without guide or monitor in the perilous realm of theological controversy. His great native force and energy of will revealed themselves in his determination to establish himself as a reformer—another aspect, it may have been, of that same creative and originative spirit which assured him an abiding place among the harbingers and heralds of scientific discovery in the still broadening field of medical research. At Basle he held conference with Occolampadius, and at Strassburg he became involved in controversy with Capiton and Bucer, the latter one of the foremost lights of the expanding Protestant Reformation, the Trinity and the doctrine of consubstantiation being the special themes involved in the discussion. These two doctrines Servetus combated with the utmost tenacity, as well as acrimony, his violence so offending his adversaries that Bucer, though inclined to moderation and self-restraint, assailed him with the greatest vehemence, even going to such an extreme as to declare that he "deserved to be cut into pieces and to have his entrails torn out" (Lib. II, pp. 56-60).

The first work of Servetus, entitled "*De Trinitatis Erroribus Libri Septem per Michaelum Servetum*," was published in 1531. He was at that time only 20 years of age. Newton was three years older when he first promulgated his theory of gravitation. Bryant, Keats, Rossetti, Tennyson produced the early poems upon which their fame in a measure still abides between 18 and 20. In his first work Servetus assails the doctrine of the Trinity, characterizing the union of the three divine persons as a mere fantasy, a chimera, gods devised by the metaphysicians. The orthodox teaching was cast aside as irrational and impossible, having no foundation save in the ignorance of theo-

logians. During the succeeding year (1532) he issued at Hagenau a second treatise relating to this subject, entitled "*De Alegoramunde Trinitate Libri Duo*," but being devoid of financial resources and having been expelled from the communion of the foremost reformed churches in Germany, he established himself in France. One of his special aims was to pursue the study of mathematics, but above all to devote himself to the science of medicine. With this end in view, he placed himself under the instruction of Sylvius and Fernel in the schools of Paris, attaining the degrees of Bachelor of Arts and Doctor of Medicine. For a time he occupied the chair of mathematics at the College of the Lombards, and in 1533 he was engaged in an active controversy with the Parisian Faculty of Medicine, the Dean and Faculty of Medicine having objected to the teaching of Judicial Astrology or Divination.<sup>2</sup> The case was carried into the Parliament of Paris, a body whose functions were judicial, not legislative, as in the English acceptance of the term, the result being a complicated and prolonged legal process which disenchanted Servetus with the French metropolis, and induced a change of residence.

We find Servetus first at Lyons in the capacity of proof-reader for the publishing house of Frelon Brothers, Mercière street, trading under the sign of Escu de Cologne. We find him later at Avignon. Thence he returned to Lyons, and finally established himself at Charlieu, where he practised his profession for three years. At the end of that time he returned to Lyons, where, meeting Pierre Palmier, with whom he had come into contact during his Parisian days, he was urged by him to make his home in Vienne, and, acquiescing in the proposal, took up his residence in this historic city, at no great distance from the Archiepiscopal palace.

The frequent changes of place which mark the life of Servetus may be attributed in a measure to the migratory tendencies of the medieval student and scholar. They were features of the intellectual life of the age. Traces of this vagrant character may be discerned in the drama of the Elizabethan era (see Hamlet, II, 2, "as the indifferent children of the earth"; also, the "*terrae filii*" of Jonson's "*Alchemist*"). In Vienne he might have passed his life in tranquillity, absorbed in the study of his profession, together with the congenial pursuit of literature as embodied in the fadeless types transmitted from the antique world, or in the novel forms, then blooming into vigorous and artistic expression under the auspicious guidance of the spirit of the Renaissance. He might have become a Sir Thomas Browne in the sixteenth century, or have been one of that rare and elect circle which mingled with Montaigne and read in their early freshness the essays which touched the thought of all Europe, fashioning the phraseology of Bacon, and contributing in at least one notable instance to the marvellous range and affluence of Shakespearean characterization. Yet no such propitious fate was in reserve for the young physician. The demon of theological controversy had entered in and assumed an inalienable possession. He had assailed the vital strong-

<sup>2</sup> Duboulay: History of the University of Paris, Vol. VI; also, account of this Academic Trial in Osler's Article on *Servetus*. Johns Hopkins Hospital Bulletin, January, 1910.



hold of the orthodox creed, and sooner or later the one issue was inevitable. Every opportunity that presented itself for the assertion of his heretical teachings was availed of with eagerness. He made frequent visits to Lyons and in 1543, while in that city, he assumed charge of a folio edition of the Bible published by Hughes de la Poite, the preface to which, written by himself, contained an exposition of his views, with marginal notes which were regarded by Calvin as not merely irreverent, but as actually blasphemous in character. Servetus again assumed the local name, Villanovanus, and Calvin mentions that he received 500 livres from the publishers for the work. (Abbé d'Artigny, *Memoirs*, pp. 65-66.) Calvin, who had known Servetus during his life in Paris, where they were both students, corresponded with him under the pseudonym of Charles Desparville, through the agency of the publisher, John Frellon. Servetus, who was not unknown in Vienne by his designation of Villanovanus, incurred not only the resentment and disapproval, but the implacable hostility of the Swiss reformer, whose creed he had assailed at a vital point in language almost unqualified and untempered in its nature. The correspondence came to a close in 1548, and Servetus addressed himself to the preparation of the work which assured his tragical fate at Champel.

To this book, known as "Christianismi Restitutio," he devoted four years and it appeared on January 3, 1553, with no indication or suggestion of either author or publisher. The book having been declined by a Basle publisher (Marrinus, by name), Servetus entrusted it to Balthazar Amollet of Vienne and to Guillaume Guérault, his brother-in-law, manager of the firm. In this epoch-making work, Servetus presents and defends his ideal religion, tracing back to the traditions of the primitive Christian age, in whose life the historic imagination reveals a unity and harmony which was in large measure the creation of its own genius. Though lacking in definiteness of language and clearness of exposition, it may be regarded as the first well-defined attempt, at least in modern times, to enunciate the principles of the pantheistic philosophy, or the doctrine of a supreme being or intelligence pervading all nature, yet impersonal in essence and in character. Emil Saisset justly assigns Servetus a place among the foremost precursors of such later oracles of the Pantheistic creed as Spinoza, Schleiermacher and Strauss. In this notable work there is revealed, despite its occasional vagueness of language and its fantasies, a conception of historic method upon which, as its basis, all the scientific achievement of a later age rests, though it was hardly even dimly descried by the explorers and researchers of the sixteenth century. From his day of dawn, it may be clearly assumed that he had been devotedly

"Nourishing a youth sublime,  
With the fairy tales of science,  
And the long result of time."

The fifth book of "Christianismi Restitutio" contains a passage in reference to the circulation of the blood, in which he announces a discovery that must assure his rank in the foremost files of scientific investigators. "La vie médicale" (August-September, 1905) has the following comment upon this

incident, forever memorable in the annals of medicine: "The first savant who saw the defects of Galen's theory was the Spaniard, Michael Servetus, who in his "Christianismi Restitutio" denied the permeability of the septum and affirmed that the blood of the right ventricle goes to the lungs where, after becoming red, it passes from the pulmonary artery into the vein of the same name." In this way, if the discovery of the greater circulation can be justly claimed by the English physiologist, William Harvey, 1615 being the date of its first announcement, and 1628 the time of its matured development, the discovery of the minor circulation must assuredly be attributed to Michael Servetus. Yet so late as 1669 the discovery of Servetus was ascribed to Lower (See R. Tigerstedt: *Zur Geschichte des Kleinen Kreislaufs, Ergebnisse d. Physiol.*, Jahrg. II, p. 533), who quotes Cheneaux and M. Roth as proving that Matheus Realdus Columbus discovered the lesser circulation and that Servetus never pursued the study of anatomy except for a short time at Paris under the guidance of Gunther.

At this point we introduce an English translation of that portion of the "Christianismi Restitutio" in which the views of Servetus in regard to the circulation are explicitly set forth:

In order properly to understand this condition of things it becomes necessary to know beforehand the substantial generation of the life spirit itself, which is composed of the inspired air and finest blood, nourished by the same (Genes. 2, 7). This life spirit has its origin in the left chamber of the heart, the lungs especially assisting in its generation. It is a delicate spirit breath, produced by the force of warmth, of clear (flavo) color, burning force and to a certain extent composed of a transparent foam formed out of pure blood and containing in its substance water, air and fire. It is generated by the admixture of the inspired air and the thinned blood furnished by the right chamber of the heart to the left. *This, however, does not take place through the middle wall of the heart, as has been hitherto supposed,*<sup>3</sup> but by an highly intricate mechanism the finely divided blood is conveyed by the right chamber of the heart by a devious route through the lungs.<sup>4</sup> The lungs prepare it for use by clarifying it and pass it from the arterial vein into the venous artery.<sup>5</sup> It is thus mixed with the inspired air in the venous artery itself and by expiration is again cleansed from soot (a fuligine).<sup>6</sup> Finally the whole mixture is drawn through diastole, serving (if I may be permitted to use the expression) as a suitable household utensil for the life-spirit.

That this preparation and assimilation takes place in the lungs is manifest by the extensive union and anastomosis of the arterial vein with the venous artery of the lung. This is confirmed by the striking size of the arterial vein, which could not have reached such dimensions and have sent the blood from the heart into the lungs with such force by its own nutritive power, nor could the heart serve the lungs in a like manner, especially since in the

<sup>3</sup> Ut vulgo creditus.

<sup>4</sup> The honor of this discovery of 1553 was credited to Lower in 1669.

<sup>5</sup> Namely, in its origin in the lungs, as will be seen later. Furthermore, that arteria venosa means the veins of the lungs (pulmon. veins) and vena arteriosa refers to the arteries (pulmon. art.) of the same needs no further explanation.

<sup>6</sup> A fuligine (from soot). This may be regarded as a purely orthological difficulty, in that the word *fuligo* formerly had a different meaning (J. C. H.).



embryo the lungs receive their nourishment from other sources. In that those membranes, or valves of the heart (in membranulos illos seu valvulas cordis) are not opened until the time of birth, as Galen has taught. For this reason the blood is poured out so profusely from the heart at that time to serve another purpose.

The lungs also send to the heart not only mere air, but such as is mixed with blood through the venous artery. The admixture therefore takes place in the lungs, not in the heart. There is not room enough in the right side of the heart to accomplish such great and thorough admixture as to render the blood clear red. Finally, the middle wall, which dispenses with vessels and other adjuncts, is not adapted for transmission and distribution, although a portion may transpire.<sup>7</sup> In the same complicated manner as occurs in the liver, where transmission takes place from the portal vein to the vena cava (a vena portæ ad venam cavam) on the part of the blood, so also happens in the lungs the transfer from the arterial vein to the venous artery on the part of the life spirit.<sup>8</sup> If one compares this with what Galen describes in Books 6 and 7 on the function of these parts, he will grasp the truths therefor, although Galen himself did not understand this (ab ipso Galeno non animadversum).

This life spirit is then carried from the left side of the heart by degrees into the arteries of the entire body, which, as they become smaller and narrower and extend upward, it becomes more diffused, especially in the plexiform tissues at the base of the brain (in plexu retiformi), where it is transformed from mere life spirit into soul spirit, in so much as it here approaches the seat proper of the reasoning soul.

And now it is still more refined, elaborated and perfected by the finer vessels or capillary arteries (capillaribus arteriis) which are found in the arterial plexuses (in plexibus choroidibus) and which contain the intellect itself (ipsissimam mentem). These plexuses penetrate the innermost portions of the brain and form a lining to the interior cerebral chambers, entwining and enclosing those vessels up to their origin in the nerves so that they are rendered capable to the sense of touch and motion. These vessels, by wonderful arrangement so finely constructed, are in reality end arteries, and hollow the course or origin of the nerves through the coverings of the brain (ministerio menengus). This is a new form of vessels.

As the merging of the veins and arteries in the lungs forms a new set of vessels composed of vein and artery, so also the union of the artery and nerve<sup>9</sup> forms a new sort of vessel from the arterial membrane to the cerebral lining, so much the more in that the covering of the brain retains its structure even into the nerves<sup>9</sup> (tunicas).

The entire first edition of this historic work was brought to Lyons. A part of it was placed on sale in the store of Pierre Merien, type-founder, near Notre Dame de Confort. Jean Frellon assumed charge of the rest. In virtue of the relations once existing between the author and Calvin, Frellon committed the fatal indiscretion of sending a copy of the newly issued treatise to the reformer. The contempt exhibited for himself and his writings, as well as the theological attitude revealed, aroused the implacable resentment of Calvin, and from that day the tragedy of Champel was a foregone result.

<sup>7</sup> Licet aliquid resudare possit: A courtesy to Galen.

<sup>8</sup> "Spirit" and "Life Spirit" would here correspond to oxygen and oxygenated blood.

<sup>9</sup> If the terms "Nervos" and "Nervis" were here replaced by venas and venis, it would afford a more intelligent understanding of the subject. Anastomosis of the arteries and veins was spoken of above, and even now the extremely fine vessels are termed "capillary-arteries."

The storm had been long gathering, for in February, 1546, Calvin had written to Farel, his co-reformer and devoted ally, that if his authority could still accomplish anything *he would never suffer him to leave there (Geneva) alive*—"vivum exire nunquam patiar."<sup>10</sup>

At this time Calvin had with him in Geneva a convert to his faith whose name was Guillaume Trie, and who was a native of Lyons. Trie maintained a systematic correspondence with Antoine Avneys, a relative of his, then living in Lyons, a loyal Catholic, who constantly and urgently appealed to Trie to return to his original belief. In February of this bodeful year (1553) Calvin requested Trie to write in his behalf to his kinsman a letter in which Servetus was described as one of the most dangerous of heretics, whether contemplated from the Catholic or Protestant point of view. The following copious extract will illustrate the character of the correspondence, and every utterance reveals the agency of the Swiss reformer:

With regard to doctrine and religion, he writes, although we enjoy greater liberty than you, nevertheless it shall not be permitted that the name of God be blasphemed, and that doctrines and bad principles be disseminated without being suppressed, and I can cite a flagrant example against you since it is necessary: namely, that they support among you a heretic who merits to be burned, wherever he goes. When I say a heretic, I mean a man who will be condemned by the Catholics, as well as by us, or at least he ought to be. For, though we are different in many things, we have this in common, that in one essence of God alone there are three persons, and that the Father has begotten his Son, who is eternal wisdom, before the beginning of time, and that he has had his eternal virtue, which is his Holy Ghost. Now, when a man says that the Trinity in which we believe is a Cerberus and monster of Hell, and vomits forth every wickedness imaginable against every teaching of the Bible with regard to the birth of the Son of God, and derides vilely all that the divines have said concerning it, pray tell me what respect would you have for him?

There is one, however, who will call Jesus Christ an idol, who will destroy all the foundations of faith, who will collect all the dreams of the ancient heretics, who will even condemn the baptism of infants, describing these as diabolical inventions; and this man will be held in favor by you and be approved as if he had been guilty of no wrong! Where is the zeal in which you exult? and where is the order of that beautiful hierarchy which you extol in such emphatic terms? The man that I am describing to you has been condemned by all the churches with which you are in accord. Yet you have even conceded him the privilege of publishing his books, so charged with blasphemies that I need make no further reference to them. The man I have portrayed is a Spaniard, by name Michael Servetus. At this time, however, he styles himself Villaneuve. His profession is that of a physician. For some time he made his home in Lyons; he now resides in Vienne, where the book I have in mind was printed by an obscure creature named Balthazar Arnollet, who established a foundry in that city. That I may not seem to speak without evidence and with positive knowledge, I send you the first page of the work as a specific proof. You profess to believe that books which inculcate any teaching save the pure simplicity of the Holy Scriptures are contaminating, and if they are in conflict with the divine word, they are not to be tolerated among you. Yet, notwithstanding, you are nourishing in your own city a poison whose aim is the effacing of the Holy Scriptures and of every teaching you have received from Christ.

<sup>10</sup> H. Tollin: Saint Vertunien De La Vau, Virchows Arch., 1885, CI, 360.



We have unfolded in this letter the first well-defined phase in the drama which attained its final stage in the autumn of this year (1553). The purpose of Calvin is foreshadowed with relentless clearness. The vision of the stake at Champel rises before the mental eye.

The Cardinal of Tournon, combining civil and ecclesiastical functions as Governor and Archbishop, had in his service at this time an inquisitor whom he had summoned from Rome, the monk Mathiew d'Ory (whose name is never recalled without a sensation of horror), who assumed the title of "Penitent of St. Siège," inquisitor in France and in Gaul. As Calvin had anticipated, the letter of Guillaume Trie and the pages from the work of Servetus were placed in his hands. With the assistance of Benoît Buatier, canon in the Church of Vienne, Archdeacon de la Tour, Camarier of St. Paul in Lyons, Vicar General of Monseigneur of Tournon, and his archbishopric in Lyons, they were rigidly scrutinized, and it was decided to report the result to the cardinal, who at the time was residing in a château at Roussillon. Buatier left Lyons March 13, 1553, and called upon him in order to advise him of the result of the investigation. Louis Arzellier, supreme vicar of the Archbishopric of Vienne, was summoned to the château, and after a prolonged conference, the two grand vicars were despatched to Vienne with a letter containing the instructions of the cardinal to Mr. Maugiron, who, after being informed explicitly in regard to the intentions of the cardinal, sent for Antoine de la Court, sheriff of the city, with a view to instituting legal proceedings against Servetus, who, in official papers connected with the trial, is always described as Michael de Villeneuve. On March 16 his home was searched, but there was nothing brought to light that implicated him, or created a suspicion of heretical teaching. The judges, impressed by the depositions made on the preceding evening before the official primate, Peyrollier, by the grand vicar and vibaille of Vienne, on the 17th sent for Guillaume Guérault, but were unable to elicit any information from him. The printers, upon being questioned separately, replied that among the books which they had printed for two years, there had been none in octavo. When the proceedings were concluded, the judges summoned to appear before them the printers, compositors and servants of Arnollet, together with their wives and servants. They were enjoined not to disclose anything that had occurred, or to make known any point in reference to which they had been cross-examined, under penalty of being regarded and punished as heretics. On the day following, March 18, Arnollet, having returned from a visit to Toulouse, was subjected to cross-examination, and made denials, the same in character as those of his brother-in-law, Guérault. The judges, in a session held at the house of the archbishop, decided that sufficient evidence had not been produced to justify or warrant the making of an arrest.

On March 19 the archbishop summoned Mathiew d'Ory, the inquisitor, to Vienne. D'Ory advised the judges that, in order to secure sufficient evidence to lead to the conviction of Michael de Villeneuve, his treatise "Christianismi Restitutio" should be examined in its complete form and not in

fragments or in passages detached from their context. To render this practicable, it was decided that the Sieur Arneys should communicate with his relative in Geneva and obtain through his agency a copy of the treatise instead of specimens or illustrations which were not sufficient to exhibit its genuine character. This measure being determined upon the inquisitor returned to Lyons and dictated the letter which Arneys was to transmit to Guillaume Trie. Through his confidential agent Calvin replied March 26, sending a greater variety of documentary evidence than was requisite to assure the conviction of Servetus, as, for example, two dozen letters written by him during his controversy with the reformer in preceding years. The proof thus furnished was supplemented by another letter, received on March 31.

On April 4 the cardinal of Tournon, the archbishop of Vienne, Pierre Palmier, the two grand vicars, the inquisitor, several ecclesiastics and doctors of divinity assembled at the Roussillon château. The documents last received from Geneva, that is, the two letters of Guillaume Trie, a copy of "Christianismi Restitutio" with marginal notes in the handwriting of Servetus, and more than 20 letters which he had addressed to Calvin, were subjected to examination. The charge of heresy was established beyond all question. Servetus was convicted upon his own testimony. By unanimous agreement the cardinal and archbishop proceeded to arrest Michael de Villeneuve, physician, and Balthazar Arnollet, publisher, and to require of them an account of their faith, as well as an answer to the charges and information laid against them.

When dinner had been finished the archbishop returned to Vienne in company with his grand vicar, and communicated to the vice-bailiff the purpose of the cardinal. In order to prevent a discovery of the plan, it was determined that Servetus and Arnollet should be arrested simultaneously and consigned to different prisons. About 6 o'clock the grand vicar approached the house of Arnollet and directed him to produce the New Testament which he had printed. The publisher appeared and was committed to the prison of the archbishopric. At the very same time the vice-bailiff (or his deputies) proceeded to the home of Maugiron, whom Servetus was attending in his professional capacity, and, advising him that there were several sick and wounded prisoners in the Royal Palace, requested him to come to their relief. Servetus replied that his duty as a physician, as well as his desire to minister to suffering, induced him to comply. They then proceeded to the Royal Prison, and while Servetus was devoting himself to his patients, the deputy despatched a messenger to the grand vicar requesting his presence. As soon as he arrived, Servetus was notified that certain charges and information, communicated to the Seigneur Cardinal de Tournon, had been laid against him, and that he was to remain a prisoner in the palace until the charges were answered, or different instructions were received in reference to his case. He was then committed to Antoine Bouin, provost and jailer, with a special injunction to guard him rigidly, at the same time according him the consideration due to his rank and his professional character. He was allowed to retain his servant, Benoît Perrin, aged 15,



who had been five years in his employ. (Memoirs, Abbé d'Artigny, p. 100.)

On the next day, April 5, the inquisitor, Mathiew d'Ory, came to assume charge of the proceedings involved in the examination of Servetus. The examination continued on the 6th, and soon after Servetus sent Perrin to the monastery of St. Pierre to ask for 1500 francs (\$300) which was due him at the Côte St. André, and the grand prieur, to whom the request had been presented, produced and paid him the amount. Almost immediately afterward the inquisitor prohibited Servetus from conversing with anyone save by special permission, and enjoined the severest vigilance upon the jailer to whose charge he had been committed. This rigorous treatment was an involuntary tribute to the generous and philanthropic spirit which was characteristic of Servetus and had won him troops of friends in every sphere of society. He had healed the vice-bailiff's only daughter of a dangerous malady; he had also restored the son of the governor, Louis de Maugiron, and during the desolating plague of 1543 he had devoted himself to the relief of the stricken. Naturally, the inquisitor feared that he might escape, and the result proved that his apprehensions were not unfounded.

On April 7 Servetus arose at 4 a. m. and asked the jailer, who was directing some work in his vineyard, for the use of the garden key. Mr. Bouin did not suspect his purpose, as Servetus very adroitly had robed himself in his night-cap and dressing-gown, which concealed his accustomed clothing, his hat being hidden by the gown. He complied with his request, gave him the key, and proceeded with his superintendence of the workmen. As soon as they had advanced a sufficient distance from him to justify his taking such a bold and daring measure, Servetus left his black velvet bonnet and furred dressing-gown at the base of a tree, leaped from the terrace of the garden to the roof below, and from thence to the yard of the palace. He reached the gate of the bridge which spans the Rhone, an ancient landmark of the Roman occupation of Gaul, extending from Pichat Square to the tower of Philip VI of Valois, opposite St. Colombe, and hastened in the direction of Givois and Lyons, as was testified by a country girl whom he met on his route. Fortunately for Servetus, she was not examined until three days after she had encountered him. More than two hours passed before his escape was discovered. The wife of the jailer was the first to be informed, and in her despair, "she gave way to every form of wild and frenzied action, such as tearing the hair, beating her servants, her children, the prisoners whom she chanced to meet, even incurring the danger of running over the adjoining roofs in her frantic eagerness to recapture the fugitive. She had been suddenly transformed into a maniac."

Every possible effort was made by those in authority to recapture Servetus. The gates of the city were closed and guarded during the night of that day and the day following. After proclamation by the trumpet a thorough and rigid search was made of all houses, including those in St. Colombe. The magistrates of Lyons and other neighboring cities in which it was possible that Servetus might have taken refuge were at once notified. They even investigated the financial condition

of the escaped prisoner by application to the banks of Vienne; an inventory of his papers, furniture, and all his personal effects were placed in the hands of the local authorities (Abbé d'Artigny, Memoirs, p. 112). On the 2d of May the inquisitor brought to light, in a remote and lonely house, the two presses which had been used for the printing of "*Christianismi Restitutio*," and ascertained from Thomas Straton, one of the employees, that he had forwarded on January 13, by order of Servetus, five packages of books to Pierre Merrin, a type-founder, living in Lyons near Notre Dame de Confort. The five packages were returned to Vienne on the 10th of May. The inquisitor prepared a synopsis of the principal errors contained in the work, with a view to emphasizing the effect of his censure or judgment by commenting upon passages detached or isolated from their context, an effective mode of distorting their meaning and perverting the teaching of the author. By the coming of June, the investigation had been completed and the following verdict was formally rendered, the text being literally reproduced from the archives of the old archbishopric in Vienne:

We, having seen the documents of said heresies, also the letters and writings of said Villeneuve, addressed to Mr. John Calvin, preacher, at Geneva, and avowed by the said Villeneuve (the said Villeneuve admitting the fact), his answers, confessions and denials, the answers and other procedures, Balthazar, the printer, agreeing, certain packages and printed books under the title "*Christianismi Restitutio*," witnesses being examined to ascertain if the said Villeneuve had written and printed the said book at his expense, the reports of D. D.'s and other notable persons concerning the errors contained in the said book and letters, which errors and heresies are, moreover, made evident when read, documents concerning escapes from prisons, and proceedings to arrest the said Villeneuve; the collected testimony, the final conclusions of the attorney of the King Dauphin, and everything considered, we have declared that the said faults have been duly obtained, in profit of which we have estopped and estop the said Villeneuve from every plea and defense; we have declared and do declare him guilty of and convicted for the offenses and crimes attributed to him, for reparation of which we have condemned him and condemn him to pay a fine of one thousand livres currency to the King Dauphin; and to be, immediately after his arrest, taken on a tumbril with his books the next day from the market of the Royal Gate through the most populous and frequented streets and places as far as the market of this city, and then to the place called Chanève, and now St. Martin Square, there to be burned alive over a slow fire until his body is burned to ashes. Nevertheless, this sentence shall be executed upon his effigy, and with it shall burn the said books.

And since we have sentenced him and sentence him to pay expenses and costs, of which we reserve the assessment, we declare all his property confiscated for the benefit of the heir, the said costs and damages claimed on this property being first paid. De la Court, bailiff and Royal Judge, Giotel, Cavier, Rutod..... assessors.

The said sentence being delivered in open court before the said attorney of the King, we, the aforesaid, sitting in court in the Royal Palace in Vienne, the 17th of June, 1553, in the presence of Philbert Gollin..... and several other practitioners of Vienne, witnessing with the undersigned clerk of the Court, Chasalis.

On the same day, June 17, the sentence was executed in effigy, as is attested by the official report of Francis Barode,



who carried it into effect, his statement having been prepared by the clerk of the court.

Our narrative now hastens to its climax. Servetus had escaped from the jaws of the Roman lion merely to be committed to the tender mercies of the relentless autocrat who dominated the civil as well as the ecclesiastical polity of Geneva. He had fled from Scylla only to be cast upon Charybdis. It may be assumed without intolerance of spirit or extravagance of language that the last state was at least not better than the first. He was arrested in Geneva on the 13th of August, while in attendance upon a religious service, and once in the hands of Calvin, the martyr's crown was a foregone result. His apparent purpose in passing through Geneva was to effect a return into Italy which, it may be supposed, still retained for him the charm that marked his early years (1523-1530) in the service of Charles V. There, too, he had absorbed those heterodox conceptions of the Trinity which heralded the way to the autumnal tragedy on the slopes of Champel.

The trial of Servetus, as conducted under the all-potent direction of Calvin, was a far more complex and prolonged judicial process than might be inferred from the ordinary accounts which have been transmitted to later ages. It extended from August 22 unto October 25, when sentence of death was pronounced against him. Nor was the autocrat and theocrat of Geneva suffered to bring his victim to the stake without vehement resistance from the party of the Libertines under the leadership of Perrin, which withstood with tenacious energy the intolerant sway and all-pervasive tyranny of Calvin, and embodied in its ranks the finest flowers of Genevan social culture, as well as the purest expression of its chivalric ideals. Encouraged and stimulated by the co-operation of so powerful a party, Servetus, who, in the earlier stages of the trial had borne himself with dignity and moderation, assumed a violent and denunciatory attitude with regard to his invincible antagonist. Yet it availed not, and despite all the efforts of Perrin, the sentence of death at the stake, pronounced on October 25, was carried into effect at 11 a. m. on the 27th.

The story of the long-drawn agony of Servetus in the flames, the rescue of his book, condemned to perish with him, his refusal to disavow his belief, even in the eye of death, his invocation with his fast fleeting breath of the mercy and compassion of Christ, have all been wrought into the historic consciousness of the ages that came after.

"He nothing common did, or mean,  
Upon that memorable scene,  
Nor called the gods with vulgar spite  
To vindicate his helpless right."

Yet in no sense can the discoverer of the lesser circulation assume rank among the martyrs to the spirit of scientific discovery. His physiological teaching seems to have been responsible for no part of the combined movement, Catholic and Protestant, that brought him to the stake. The demon of theological speculation had entered his soul and the demon of theological intolerance pursued him with its unique and unrelenting malignity until there remained no trace of Servetus in the world, save scattered ashes, a name from that time famous,

and a mournful memory. In assailing the doctrine of the Trinity inculcated with invincible devotion by the whole Christian communion, he had left himself no sanctuary or asylum; his attitude was one of hopeless, irreclaimable isolation. To impugn the orthodox creed in this special phase of belief constituted an offence against both the civil and ecclesiastical code which involved grave consequences and placed the offender in a category not unlike that assigned to an anarchist or a dynamiter as contemplated from the viewpoint of our modern civilization. Sadducees and Pharisees, the society of Jesuits and the theocratic forces marshalled by Calvin, made common cause against their common enemy. The Catholics burned Servetus in effigy at Vienne; Calvin burned him in reality at Geneva. One was the preluding rehearsal, the other the ghastly tragedy.

In addition to his heretical attitude with reference to the Trinity, Servetus had been imbued with the teachings of the Anabaptists; he strenuously repudiated the doctrine of infant baptism and was involved in the odium attaching to this widespread sect whose name was almost a symbol for licentiousness and disorder. Against the combined forces of Trinitarian orthodoxy, the attempts of the Libertines to pluck Servetus from the grasp of Calvin recoiled as vain and impotent.

A determining element in sealing the doom of Servetus was the critical condition of the Protestant reformation during the years contemporary with the final period of his activity, or, to express it in other terms, the period which marked the middle of the sixteenth century. The outlook for Protestantism was dreary, it might be even hopeless. The Marian, or Roman Catholic, reaction in England dates from 1553; the Society of Jesus was undoing the work of the Reformers with seemingly resistless energy; Geneva was confronted on the one side by the Valois monarchy; to the North was the empire of Charles V; and Luther had been dead for seven years. The isolation of Calvin was almost complete; "a pillar steadfast in the storm," the last refuge and stronghold of the cause of Protestantism. The escape of Servetus would have implied a fatal weakness on the part of Calvin and his colleagues. The issue was not personal, not local—it was all-embracing in character, and in the result was involved the very life of the Protestant reformation.

That his scientific or physiological teachings were not introduced as an element of antagonism to Servetus reveals one of the most suggestive phases of his strangely dramatic and almost unique career. The question seems never to have been presented save as containing another form of heresy. The theological aspect of the controversy was the exclusive issue, for the oracle of Geneva, Calvin, despite his austerity of nature and inflexibly dogmatic temperament, was endowed with a sense of literary and scholarly appreciation that has won for him no inconspicuous rank in the records of linguistic evolution during the sixteenth century. He was not indifferent to the charm of science or hostile to its development. In marked contrast to the spirit which asserted itself at the time that William Harvey first announced his discovery (1615), he would not have condemned Servetus for his theory of the



lesser circulation. Harvey incurred financial loss by the promulgation of his novel views, and it is said that they were not accepted by any physician beyond the age of 40. When they were given to the world in their matured form (1628) they appear to have gained favorable regard by slow degrees, and in 1633, when Giles Fletcher published his "Purple Island," the "thousand brooks," representing veins and arteries, were described in accordance with the ancient doctrine, in apparent ignorance of the discovery of Harvey.

The charge of plagiarism which has been suggested with regard to the scientific teaching of Servetus<sup>11</sup> need not be dwelt upon here further than to say that it is groundless. His mind seems to have been marked by rare originality and creative power. A vein of mysticism and a touch of poetry reveal their influence in his style; the sensibility of his Spanish nature at times shines through the dialectic dreams and reveries of the work that attained its logical climax at the spot now designated by the monumental granite block (dedicated November 1, 1903) which constitutes the Expiatory Monument.

The strongly developed anti-dogmatic tendency of Servetus suggests many parallels and analogies in varying ages and under diverse historic conditions. Perhaps no one of them is presented in stronger light than Archbishop Whateley, whose attitude in reference to the dogmas formulated by theologians exhibits a striking resemblance to that enunciated by the antagonist of the Swiss reformer. The execution of Servetus was regarded by the contemporary theological world as a vindication of truth and a triumph of righteousness. The entire Protestant communion approved the deed; the gentle Melancthon was especially emphatic in his expression of concurrence. In no sense did Calvin regret or repent his action. On the contrary, he acquired new strength and influence as the champion and vindicator of the Reformation against heresy. The Church of Rome could not longer exercise the sole prerogative of inflicting vengeance upon the enemies of the Gospel. Scandalized, as Gibbon naturally was more than two centuries later, by the burning of Servetus, it none the less remains an invincible truth that Calvin concretely represented the dominant religious ideals and the purest political aspirations attained by his own era.

It is a notable historical fact that the penalty of death for denying the doctrine of the Trinity was inflicted in Protestant England during the reign of James I (1611),<sup>12</sup> long after Calvin and Servetus had passed to their account, and that while the statutes which defined its character became gradually void and inoperative with the growth of a tolerant spirit, they were not formally repealed until a time that is strangely and suggestively near to our own era, with its tendency toward anti-

<sup>11</sup> This matter has been thoroughly investigated by the author in his "History of the Circulation of the Blood—Contributions of the Italian Anatomists, Psychologists, etc.," Johns Hopkins Bull., 1905, May, Vol. 16.

<sup>12</sup> The "Atheism" of Sir Walter Raleigh and the "Arianism" of John Milton and Sir Isaac Newton are suggestive to the student of science as well as to the student of literature.

dogmatism, if not toward indifferentism and agnosticism—the negation of all definite or positive belief.

The Expiatory Monument, erected by the combined efforts of the Reformed Churches of France and Switzerland and dedicated with impressive ceremonies Sunday, November 1, 1903, occupies a position perhaps unique in the records of the Christian religion, if not in the annals of the world. Monuments have been reared by societies or representatives of ecclesiastical organizations, in order to embody in abiding form their expression of repentance and contrition, elicited by the consciousness of grievous wrong or atrocious persecution inflicted upon opposing faiths, or upon antagonizing systems and beliefs in the sphere of philosophy or in the province of political polemicism. The long-deferred confession came from the successors or representatives of the creeds which were involved in the act in its original intolerance. The attitude of the monument at Champel is one of complete isolation. It has no prototype or counterpart in all records. It was created by the co-operative efforts of those whose religious ancestors had wrought the deed of shame, by loyal successors of Calvin devotedly attached to the cardinal teachings of the Reformation of which he was the vital force, and which, in its critical moments, he plucked almost from the grasp of despair. The granite block is not merely distinguished from every other monument of which the ages hold record, it stands aloof even from the other monuments erected to perpetuate the genius and the achievements of Servetus. By no means the least of the claims to honor and renown which are the inalienable prerogative of the medical profession is the simple reminder that this phenomenal tribute of the modern spirit had its inspiration and its outcome in the life and labors of a physician. The motto of the city of Geneva, "Post Tenebras Lux," seems to reflect an undreamed-of radiance of meaning, as we contemplate the massive granite hard by the Church of St. Peter, in which Calvin was accustomed to preach and where his memory is still held in reverence, perhaps more discerning and rational in its nature, as the world with resistless gravitation sweeps into the younger day.

"Doctrina sed vim promovet insitam,  
Rectique cultus pectora roborant;  
Utcunque defecere mores,  
Indecorant bene nata culpa."

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## THE PSYCHOSES OF THE HIGH-IMBECILE.

By HENRY J. BERKLEY, M. D., D. Sc., Baltimore.

Generalizing, it is well to remember that the high-imbecile from the cradle onward develops slowly; that he is behind the normal child in learning to walk and to talk; that in attention as well as imitation he is backward, and that when childhood begins and school life opens he shows up as a dullard or one-sided individual. In his habits he is negligent and untidy, and is often the sport of better endowed companions, an item that has a bearing on the whole of his future life. In his class-life he is in constant conflict with his teachers, to whom he is a despair.

The final scholastic attainments are, as a rule, a superficial knowledge of reading and writing. Spoken language, on the other hand, is often voluble, though it will be found on examination that the vocabulary is limited, and that scanty ideas are submerged in a torrent of oft-times meaningless words. Few are at all proficient in arithmetic, even those who have had a fair opportunity of obtaining a good education; with the automatic indrilling of the multiplication table their ability ends; subtraction, division and compound multiplication remaining an unfathomable riddle. Many fluent in language cannot tell the hour by the clock, and in abstract deduction of a simple problem they show no reasoning ability.

When the age of adolescence is attained the rise of the sexual instincts, as well as altered conditions—the increased personal liberty and freedom from restraints formerly imposed by parents and guardians—seem to aggravate all their propensities for evil; excesses of all kinds are now indulged in.

At this period lues is often acquired and plays an important part in their subsequent mental degradation, but, in the majority, inebriety has an even more prominent rôle in this respect. Few are there among the high-imbeciles that do not show its after-effects when psychoses develop, as is evidenced by the hallucinations and the delusions of persecutory cast.

In the list of delinquencies thefts are frequent, to obtain the necessities for future pleasures; rapes are usual when money or means are lacking to attract the weaker sex; vagabondage and mendicancy are common, so that children of respectable parentage are found harboring with thieves and prostitutes to their own detriment as well as to the scandal of the community in which they live.

Not infrequently, after a course of dissipation, the defective inherited protoplasm comes to the succor of the family pride. A few months of excesses and the hereditary weakling becomes passive, inert and unable to take care of himself; in other words, he becomes demented, and seeks the sheltering walls of an institution, to be cared for to the end of his days.

There seems to be some law of premature senescence descending upon members of the imbecile class about the age of adolescence that renders a future development of viciousness as well as licentiousness impossible—an impossibility perhaps due to some conflict between the correlation of the internal secretions. In any event, the mental development comes to a

stand-still, with eventual retrocession; it may be after the lapse of only a few months. It should be remembered in this connection, as having a direct bearing upon the subject at issue, that the age of puberty and adolescence is the most trying period in the evolution of the higher cerebral association fibers, rapid growth of the body occurring with advancing maturity of the sexual system, and in these individuals the cytoplasm necessary for successful development is both deficient and defective. Hence a rapid decline of the neural vitality and a terminating mental reduction.

Alcoholism, syphilis, the excessive use of tobacco, late hours, as well as over-drain upon the sexual organs, all play a decided and important part in the immediate mental downfall of the defectives. Few examples of hallucinations are found without some antecedent history of alcoholic misuse.

The stigmata of degeneration in the high-imbecile class are much less frequent and pronounced than in the lower types; the physiognomy is less explicit in its tale of intellectual barrenness. In fact, many of the so-called moral, emotional or impulsive cases are sufficiently high in the intellectual scale not to portray to the untrained mind their actual degree of weak-mindedness and, accordingly, among the masses, they pass for normal individuals. It has been said that clothes make the man and certainly a well-groomed individual offers less to the eye that is suggestive of mental defect than those that are unkempt and untidy. But, by examination with the Binet method, or with the simpler arithmetical tests, together with questions as to judgment and insight, a fair knowledge of the degree of mental endowment may be ascertained within a few minutes, and the results are often surprising, showing as they do an incompetence that was entirely unsuspected from the surface.

The psychoses of the moron class are extremely varied, complicated, interesting, and have not been sufficiently studied, mainly because the majority of mental workers have not been taught to recognize the imbecile in his highest development, when he stands nearest to the normal man; and although they recognize that in certain cases running the course of an atypical catatonia, hebephrenia or early dementia the patients are of sub-normal mental grade, they lay but little stress upon this fact.

Grading carefully from the lower types of imbecility to the moron group, the last showing but few physical and still fewer gross psychical defects, we find that a high percentage of the permanent inhabitants of institutions (excluding seniles and paretics) have a defect in their mental gearing of the most varied degree and characteristics, with which is coupled a psychosis.

Naturally, the insanities of the high-imbecile fall among recognized types of adolescent psychoses, but at the same time and in endless variety they depart from classical cases of these maladies in symptomatology and duration.



Tabulated, we find cases in the clinic resembling:

- (1) The dementia præcox group.
  - Catatonia.
  - Hebephrenia.
  - Paranoid forms.
- (2) The alternating insanities.
  - Periodic and circular forms, with pathological exaltation and depression.
  - Stuporous states, either simple or alternating with motor excitement.
- (3) The dementia group.
  - Dementias progressive in character, without depression or exaltation of any duration.
- (4) Cases with especial disturbance of hearing, sight and gustation.
  - Acute and chronic hallucinosis.
- (5) Cases that are especially characterized by the presence of false ideas.
  - Acute and chronic delusional states.
- (6) Cases whose principal feature is the occurrence of impulses or impellent acts of a pathological nature.
  - Obsessions and pathological impulses.

But the course of the first two of the above divisions does not follow closely the cardinal types. Most notable in all of them is the tendency toward a quick dementia, which is final and often complete, but even to this rule there are certain exceptions, especially among individuals showing a simple motor excitement free from delusions and hallucinations.

Another difference lies in the short course of the malady in contrast to the longer duration in the typical cases of catatonia or periodic insanity. In the high-grade imbecile the psychoses end after a few days or weeks in a quick return to the former mental state or in an equally rapid mental reduction and passivity.

Furthermore, and as a cardinal point, the onset of the psychosis is more sudden and without the preliminaries of the catatonic or manic-depressive types; the attack is briefer, the return to former mentality more complete within a shorter space of time. In the absence of alcoholic abuse hallucinations are rare.

Returning to the above classification and simplifying it to a certain extent, we find:

(1) *Cases of Pathological Exaltation, with the Features of Short Course, Rapid Termination in a Dementia or Return to the Former Mental State.*—These forms of excitement are common, especially with adolescent youths and are uncomplicated by alternating depression or hypochondriacal fancies; in fact, delusions themselves are infrequent or of the simplest character. The outbreak of the malady is characterized by a sudden onset, violent as well as extravagant tendencies, logorrhea with incoherence in the assemblage of ideas, also by a varying degree of intellectual confusion during the period of excitement, this passing sometimes into actual stupor, out of which the patient returns to his normal state. In this class, on the whole, the motor are more pronounced than the mental symptoms. The duration of the entire seizure is short, a few days, infrequently a few weeks, with restitution or dementia according to the strength of the inherited protoplasm. Attacks in those fairly

endowed are liable to be repeated from time to time; occasionally a patient is seen that has had only one, though he may suffer at times from irritability not amounting to an actual psychosis.

(2) *States of Pathological Exaltation in Individuals of a Slightly Higher Mental Grade than the Preceding Class.*—With thought confusion are now mingled delusions of pronounced but varied character. Dependent upon abuse or non-abuse of alcohol their content varies from simple delusions of personality, surroundings, power, wealth, and above all, those that belong to a perverted egoism, to varied delusions of persecution, mainly attributed to persons with whom they have been in contact in their own household or at the work-shop. These false ideas are systematized to the extent that they do not vary greatly from day to day and may last for many weeks. Hallucinations even in moderate alcoholics (or cocaine habitués) are usual. Those of hearing are of a persecutory cast, unfriendly voices telling them that they are foul with syphilis; are no longer men; that their wives are unfaithful. Those of sight are also frequent with this class. They see figures or pictures moving in the trees. God or the devil appears and commands them to do certain acts. Hallucinations of being covered with creeping vermin, that burrow through their flesh, are also common. Gustatory deceptions are less frequent.

In the case of the majority of the individuals of this class one attack brings them to the asylum and, although they may recover to the extent of becoming quiet and manageable, the finer part of the faculties is blunted, and they are no longer capable of returning to their vocations or, unassisted, of attaining to any steady employment, though they may do fairly well under the guidance of another and stronger mind. Eventually they slowly descend in the mental scale or, after repeated attacks, become completely fatuous.

(3) *Cases that show a variation from the second type, in so far that, after a period of moderate pathological hyperactivity, with delusions and frequently hallucinations, deep confusion begins, ending in stupor with catatonic rigidity, negativism, as well as resistance to passive extension of the extremities.* The circulation is low, the heart's action feeble, the extremities cyanotic, and the vitality falls to a low ebb. Death occasionally occurs in this state of stupor, without any return to consciousness. In the depths of the lethargy the quivering eyelids are the only signs of life; the pupils are widely dilated, the face is pallid, while the respiration is slow and uncertain.

In the less severe cases partial restitution takes place within a period of two to four weeks, the victim no longer requiring to be tube-fed and being more energetic; but the delusions continue unabated, slowly to fade in the darkness of a dementia that is final.

(4) *Paranoid tendencies* are frequent with the high-imbecile. Alcoholism and masturbation are the foundation stones, in common with other agencies of a depressant nature. In the brain of the three-quarter wit, probably after a series of misfortunes, mainly owing to his incompetence or inattention to duties, there comes to be evolved the idea that the hand of mankind is against him; that he is being kept down by favor-



itism toward others and robbed of his proper deserts. The essential egotism of individuals of the moron class, deep-lying and always ready to take offense, when errors of omission or commission are corrected, renders them unduly sensitive to the "blows of unrequited fortune"; they sink more and more within their inner selves; introspection, with alcoholic excesses, soon lowers the mental vitality; false ideas that they are objects of persecution or sport by their fellow workmen arise; soon aural hallucinations are added to the delusions that they are the subjects of unwarranted hostility from their fellows; unfriendly voices assail them, coming from whence they do not know, as they reach them on the street or in the quietude of their own abodes. Soon attacks on employer or fellow-workmen supervene, the police interfere, and the gates of the asylum open.

After entering an institution the mental downfall is usually rapid. At first voluble with their complaints to the medical men or attendants of the institution, there is soon a withdrawal from association with other inmates and an intensification of the persecutory ideas, which is followed within a year by a deeper and yet deeper dementia, though this class rarely becomes so fatuous as those of the first divisions.

(5) *Cases Resembling the Alternating (Manic-Depressive) Insanities.*—From the narrow egotism of the moron class it may readily be imagined that examples of real depression are far less frequent than those of excitement and stupor, the true periodic cases standing on a higher plane of mental altitude. Like the states of excitement of the first and second classes, they show the same sudden beginning with few antecedent preliminaries, short course and ordinarily rapid termination. With the majority that fall under this category, the stage of excitement is marked by a deeper clouding and confusion than is usual with the typical manic depressives; ideation is shallower and delusional ideas more pronounced. Motor agitation is sometimes well marked; at other times trivial. The periods of depression show energy rather than delusional depression, while the mental level of the entire psychosis impresses one as being more grave as well as more irremediable than in pure alternating examples.

(6) *Stuporous states*—not the occasional stuporous conditions of the periodic or of the catatonic, but of a character quite apart from these, and manifesting but little of their symptomatology except for the more prominent element. In the moron instances of simple stupor, except with women at the time of menstrual periods, are rare. With little disturbance of the vital functions and still less of delusional or hallucinatory implication, these individuals for a short time become irritable, restless, or as they express it, "nervous"; then suddenly they pass into a deep passive sleep, out of which nothing in the way of varied stimuli can arouse them. They require to be tube-fed and in every way looked after. After the lapse of from ten days to two weeks they suddenly, often in the early hours of the morning, come out of the realms of night into those of day. During this state of total anergy there are no muscular movements, no negativism, nothing approaching a cataleptic condition; only passivity. The pupils are widely

dilated, the pulse slowed, the respiration tranquil but shallow. The temperature is usually sub-normal. The tendency is to recover after a time, but, contrary to what happens in the preceding varieties, the malady is not customarily followed by a mental decline, except when the attacks have been repeated over and over again. Questions, after recovery, as to their recollection during the phase of stupor, ordinarily elicit but little information. Some refer to it as a prolonged uncertain dream; others have no distinct remembrance at all.

(7) *Progressive Dementia Without Active Motor or Psychic Symptoms.*—Not a great many cases coming under this category have fallen under my notice. The majority were not high in the mental scale, and some had the brand-marks of an inherited syphilis. Spinal fluid tests were frequently positive.

In the earlier stages there comes a time of ill-defined nervous agitation without definite delusions or hallucinations, after which the subjects slowly dement without further active symptoms. Not a few examples show the evidences of a chronic arteritis, sometimes luetic, sometimes of other types, and as definite histories are frequently lacking, it may be presumed that some have suffered from typhoid or other infectious fevers which, together with the after-effects of the accompanying irritant toxin, has induced a chronic state of nutritional defect leading up to the psychosis. The general bad effects of licentiousness in this class have already been considered.

With a number of ill-balanced children, who have been forced to undertake a school education ill-suited to their strength and mental endowments, the continued strain of years of effort results at the time of adolescence in a mental decrepitude from which after-treatment is powerless to rescue them, and they descend slowly to the plane of the dement.

In the first stages there is a period of ill-defined restlessness with depression, passive in nature, but without delusions, hallucinations or motor excitement. Soon this restlessness passes away and is succeeded by a dull apathy, the victims taking no interest in anything about them, remaining dull-eyed to questions or stimuli of varied nature and not even reactive to loud noises or pin-pricks. All day long they sit passive on the benches with bowed head and drooping shoulders, eyes directed to the ground, unseeing, with hands livid and oozing sweat and so remain for months until removed by a pneumococcus or colon bacillus infection.

In addition to syphilis and infectious diseases, it may possibly be that a lack of correlation between the internal secretions is again a principal factor in this passive dementia. Not a few have deficient thyroids and occasionally one may feel in the lobes of these organs little hard nodules that are abnormal.

(8) *Chronic states of delusion and hallucination* are mainly attributable to the after-effects of drugs and especially of alcohol. Auditory hallucinations are of more importance than visual ones, as they exert a deeper impression upon the sufferer, being but reflexions of his abnormal thoughts, and accordingly are not so readily corrected. These false ideas and sense fallacies are in a measure permanent, fixed, in a crude way systematized, have a persecutory cast and materially influence the lives of individuals, becoming to them the most



prominent feature of their daily life, as well as influencing all their actions. Eventually they lead up to attacks upon others or to suicidal attempts. Insight and judgment are seriously affected and at last there begins a noticeable degree of dementia, which deepens as the months advance, the sensory fallacies becoming less and less prominent until eventually lost in the mental clouding.

We especially desire to call attention in this paper to the fact that the high-imbecile is far more prone to the psychoses than a man of higher mental development; that practically all forms of simple and complex mental disorders are to be found among them, though a number are represented in simplified form; that the pernicious action of alcohol in particular, as well as of other drugs, although in less frequency, is much more marked in them than in normal man and is, in fact, the corner-stone of the vast majority of their hallucinations and delusions; finally, that few make a complete recovery from any of the forms of psychosis above enumerated, a terminal dementia of quick onset being the rule.

One addendum we desire to make to this article before closing. It is an inflexible law of Nature that like can only produce like. The high-imbecile reproduces his kind and, unrestrained by ethical laws as well as by care of the future, in ever-increasing numbers; the progeny to be an increasing burden upon the

tax-paying community, as well as a sore strain upon the up-keeping of the law. If we leave this portion of the population to increase unrestrictedly and at an unnatural rate in proportion to the total increase of the population, one result is inevitable: they will eventually overwhelm by sheer numbers the producing people and the race will then sink to a low level.

I am reminded of a short story read some years ago, depicting the earth a thousand years hence. According to the author some fearful cataclysm had overwhelmed the entire world, leaving but few of its folk, and these soon degenerated. It is true they multiplied in numbers, but they further descended in the mental scale to below, far below, the rapine beasts of the field. Fire they knew not; war and slaughter were their only arts; while cannibalism was prevalent. Their only science was to destroy.

The only solution of the problem of the high-imbecile is sterilization; a general law affecting all the states should be enacted compelling the castration or spaying in all educational institutions or asylums for the insane or defectives of those who are capable of reproducing their kind. Many physicians are opposed to such a law, mainly on the ground that it might produce an increase of venereal diseases, but these considerations are of minimal importance compared with the general deterioration of the entire race. *Salus populi suprema est lex.*

## A DERMOID CYST SHOWING UNUSUAL FEATURES.

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*(From the Dermatological Clinic of The Johns Hopkins Hospital Dispensary.)*

### CASE REPORT.

J. C. N., a negro, aged 40 years, presented himself for treatment at the Dermatological Clinic of The Johns Hopkins Dispensary in March, 1913.

Just to the left of the center of the forehead was a small round tumor about 7 mm. in diameter, which clinically presented all the features of an ordinary sebaceous cyst. It had been present four years and showed the usual comedo-like opening. It was smooth, freely movable over the deeper structures, and had shown no recent rapid increase in size. Some months previous to the appearance of the tumor, a long lanugo hair had developed at the point, which later was shown to be the site of the comedo-like opening of the cyst.

The accompanying photomicrographs show well the unusual microscopic appearance of this tumor. The comedo-like opening is seen to connect directly with the cyst, which is filled with layers of horny substance and numerous lanugo hairs. At various places from the cyst wall diverticula, containing horny material and coiled-up hairs, extend out like pockets, into which open one or more hair follicles.

The epithelium of the cyst wall is similar in most respects to the epidermis of the skin with which it is continuous. The pigment, however, of the rete cells of the epidermis extends only through the comedo-like opening and is not present in

the epithelium of the cyst wall proper. The granular layer of the epidermis, however, is found in a most modified form throughout the epithelium of the cyst wall. Papillæ, such as occur in the true skin, are absent.

The most striking feature presented by the cyst is the large number of modified hair follicles which spring from all parts of its wall. The hair follicles begin as short, thick pedicles, which very quickly branch into short finger-like processes, many of which contain lanugo hairs. It can be very definitely shown, either in a single section or by serial sections that these hair-containing follicles branch, and that at times two or more hairs are contained in a single follicle. Springing from these hair follicles and at times directly from the cyst wall are other finger-like processes which do not contain hair, nor have they a lumen, although their cellular elements resemble in every way the cells of the hair-containing follicles. It is a question if these processes represent developing hair follicles or rudimentary sebaceous glands. No definite sebaceous glands are present.

### GENERAL CONSIDERATIONS.

It seems to be far from proven that a congenital tumor, formed by the snaring-off process, can be connected with the surface by an opening such as occurs in this case. Török,<sup>1</sup> in



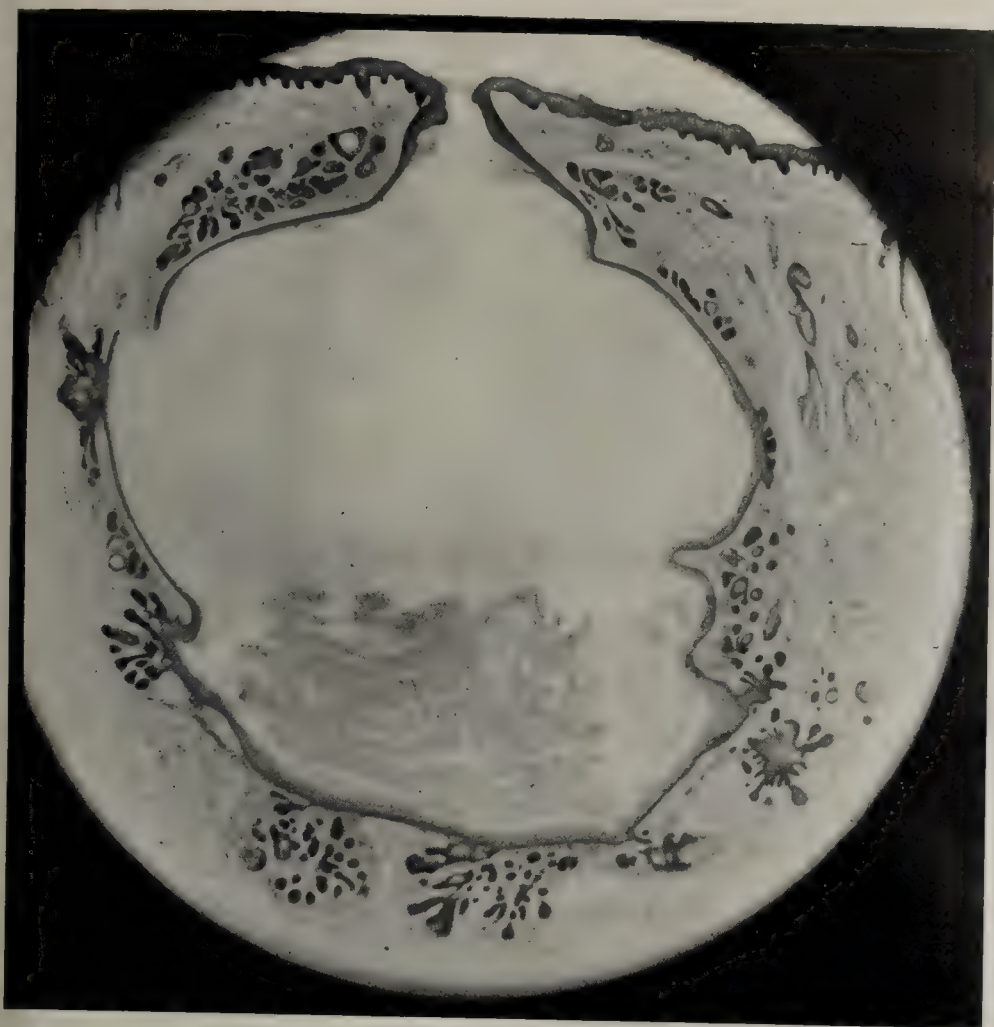


FIG. 1.—Vertical section through cyst showing opening to the surface and groups of branching hair follicles growing from its walls.

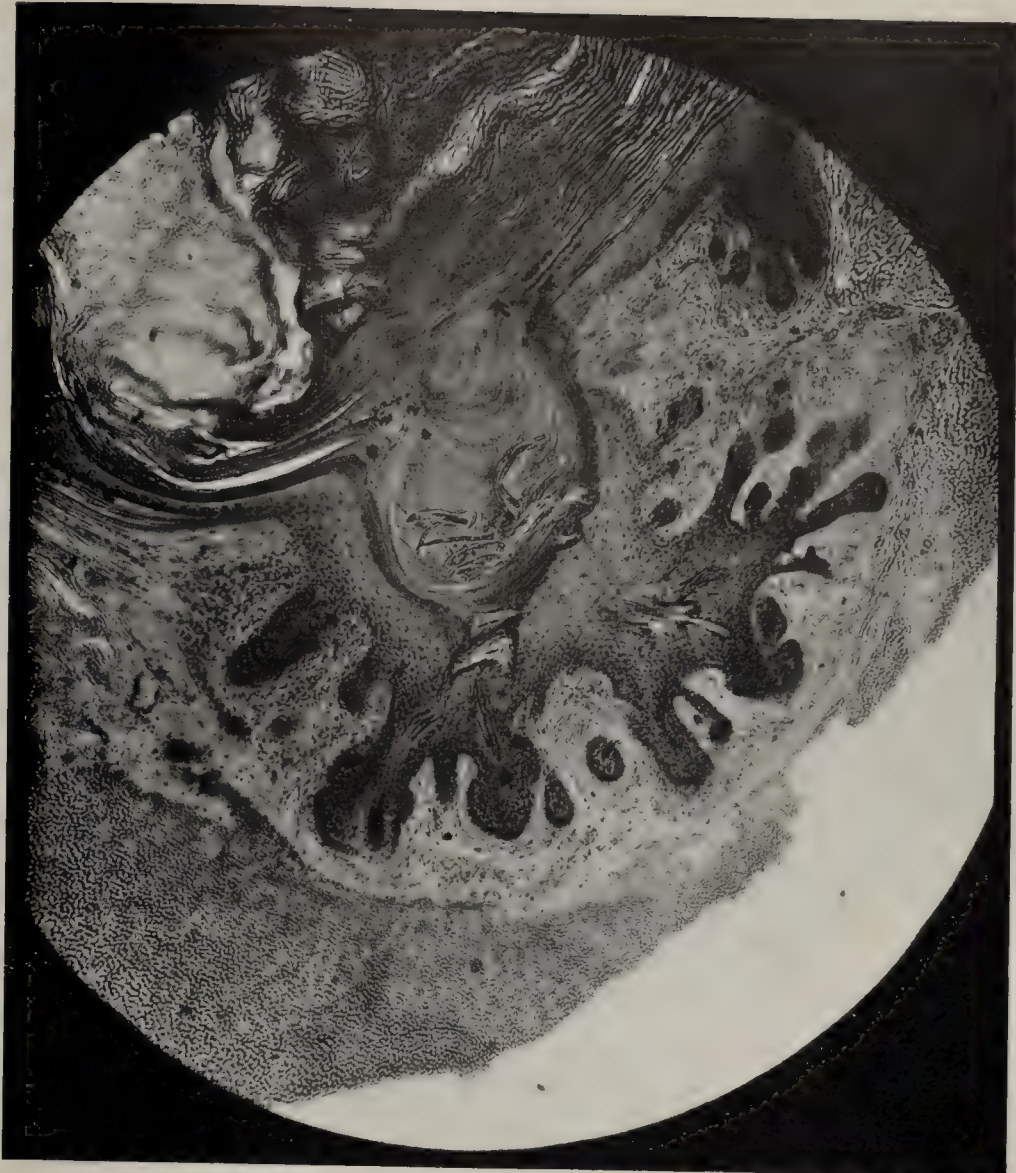


FIG. 3.—Diverticulum in the walls of the cyst filled with hair and horny material and from which branch out a number of hair follicles.

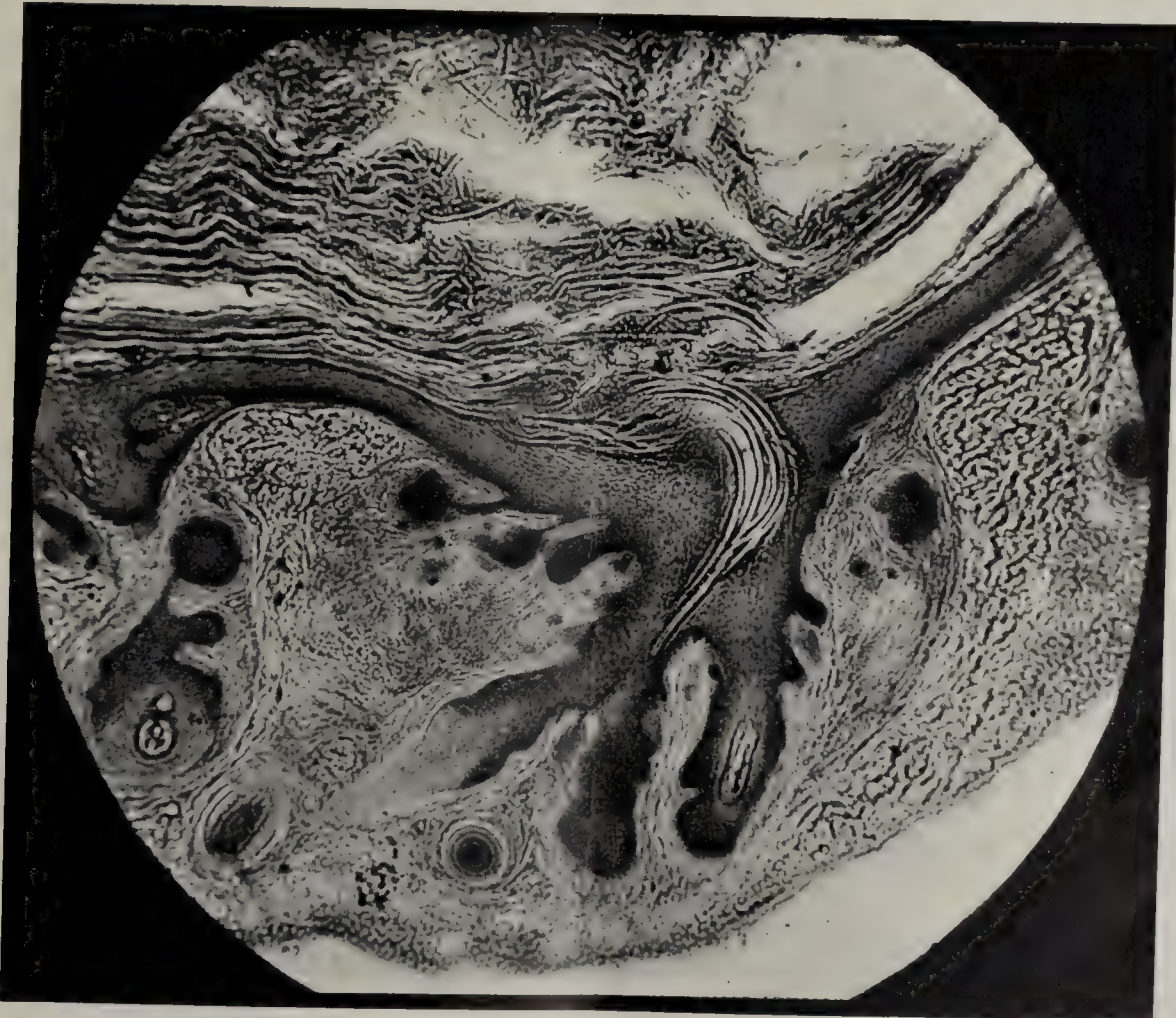


FIG. 2.—Section showing an enlarged branching follicle containing multiple hairs







1891, reported such cases, but Unna<sup>2</sup> considered them "doubtful specimens." These cases showed some hair and sebaceous glands, both of which might occur in ordinary retention cysts. Török considered them as instances of congenital cysts, chiefly on account of their location, contents and the presence in their walls of ordinary skin papillæ. These criteria are of value when taken with other evidence, but by themselves are not conclusive (Unna<sup>2</sup>).

In the cyst here described we have a highly specialized structure, namely, the hair follicle, of which the anlage, at least, must have been present at birth. As hair follicles normally occur only in the skin, therefore, at least a sufficient portion of epithelium, containing a number of anlagen of hair follicles corresponding to the groups of hair follicles in the cyst, must have been invaginated from the surface during foetal life. Such specialized structures could develop from a cyst in no other way. Although hair follicles are prone to develop epithelial buds, it is inconceivable that such buds should develop during middle life into specialized structures such as hair follicles.

One must, therefore, come to the conclusion that this is definitely a congenital cyst of the dermoid type. Why the opening has remained is difficult to explain. The simplest and most probable explanation is that the lanugo hair, which appeared several months before the tumor, forced its way up through the surface epithelium as a result of the activity and growth which commenced at that time. This explanation is strengthened by the appearance in the scar, some time after the operation, of a lanugo hair, the follicle of which, as serial sections showed, was a lateral branch of the cyst which had not been entirely removed and, continuing to grow, had forced its way through the surface epithelium. If this hair could thus penetrate to the surface after the operation, there

is no reason to question its ability to do so before the cyst was removed. This would have been the more easy to do if the foetal invagination had been incomplete and a pedicle of epithelial cells had remained connecting the snared-off portion with the surface. In the healing of wounds, in which the upper portions of hair follicles have been destroyed, the continued growth and development of the follicle can take place<sup>3</sup>.

A study of the sections shows that the different hair follicles are in all stages of development, which suggests that only the embryonic fundamentals, or, at most, very early stages, of all or most of the follicles, were present when the tumor began to grow four years ago. At this time the follicles began to develop and enlarge and, as a result of this activity, there was formed the horny material and the hair which go to make up the tumor mass.

#### CONCLUSIONS.

The tumor, then, was a congenital or dermoid cyst showing definitely a comedo-like opening to the surface of the skin, remarkable because of the numerous groups of hair follicles branching out from the cyst wall. Its germ or anlage no doubt consisted in a simple epithelial invagination, enclosing a number of anlagen of hair follicles, which were formed during early foetal life, either before or after the hair follicles had begun to develop. In either case the further development was probably arrested after this invagination had taken place and was resumed only in adult life at the time the tumor formed.

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## THE MECHANISM OF LABOR IN SPONTANEOUS EVOLUTION.

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From time immemorial it has been recognized that neglected transverse presentations are associated with an excessive maternal and foetal mortality and this belief became accentuated after the researches of Bandl and his successors had made us familiar with the physiology of the lower uterine segment and the mechanism of rupture of the uterus. Consequently, all modern obstetricians teach that for practical purposes transverse presentations are not susceptible of spontaneous delivery and urgently demand operative interference. This consists in version and extraction of the foetus, if the patient is seen before the uterus has contracted tightly down upon its contents; or in decapitation, if the shoulder has become so firmly impacted in the pelvis that version is either impossible or promises to be attended by such risk of traumatic rupture of the uterus that an attempt to effect it is not justifiable.

This being the case, competent obstetricians no longer feel justified in pursuing an expectant course in the presence of this abnormality; consequently, they have an opportunity of seeing what nature may occasionally accomplish only when patients come into their hands after having been neglected by ill-trained physicians or midwives.

At the same time it is well known that spontaneous labor may occasionally occur in transverse presentations under conditions which ordinarily would appear to be desperate. Such an outcome may be effected in one of three ways: spontaneous version, *partus conduplicato corpore*, or spontaneous evolution. The first eventuality, which was described by Bartholin in the 17th century, usually occurs in the first stage of labor before the cervix has become fully dilated and usually before rupture of the membranes. It results in the gradual rotation of the child about its long axis in such a manner as to bring



either the head or the breech into relation with the superior strait. In this event the child is born by the head or by the breech by the usual mechanism, and there is nothing about the subsequent history of the labor to indicate the seriousness of the original situation.

*Partus conduplicato corpore*, or birth with the doubled body, was first accurately described by Roederer in 1756. Since then it has been frequently observed, and is generally admitted to be possible whenever pregnancy is terminated at a period when the foetus is sufficiently small to permit both its abdomen and thorax to pass through the pelvis at the same time. Consequently the mechanism is usually observed during the premature birth of a macerated foetus.

Spontaneous evolution, on the other hand, may occur when the child is well developed, and is a complicated process in which birth is effected with the shoulder remaining the presenting part. Such an outcome was described by Denman in 1772 and by Douglas in 1811, and requires an elaborate mechanism, which is possible only under exceptional circumstances. Following the first observations of Denman, numerous examples of spontaneous evolution have been described, but even at the present time the statements of authoritative writers as to the details of the process do not correspond and a great deal of confusion still exists.

In this paper I shall describe two cases of spontaneous evolution which occurred during my service as resident obstetrician at The Johns Hopkins Hospital, and afterwards I shall consider some of the disputed points in connection with the process. I am obliged to confess, however, that it will not be possible for me to solve the problem in a thoroughly satisfactory manner.

CASE I.—*Spontaneous Evolution from R. Ac. D. A. S. S.*, House No. 5108, October 24, 1911; 27 years old, Russian, married four years. Has had four spontaneous labors, and is uncertain as to the date of the last menstrual period. Pelvis normal; measurements 26, 28, 30, 21.5 cm., D. C. 11.75 cm.; arch fair, tubers. 9.75 cm.

The patient was first seen by the out-patient obstetrician at 10 p. m., when the following history was obtained: Pains began at 3 p. m. Soon afterwards the membranes ruptured spontaneously and a *foetus compressus*, 16 cm. long, was passed. After this the pains were strong and frequent, and at about 7 p. m. the midwife found a hand in the vagina. She called a physician, who confirmed her diagnosis of transverse presentation and sent to the hospital for assistance.

When seen by us, the patient was having severe pains at two-minute intervals. General condition good. External examination was unsatisfactory, owing to almost tetanic contraction of the uterus. Foetal heart not heard. On separation of the labia a hand was visible, but it was too high up to be identified; a few minutes later it came into view and proved to be the left hand. Rectal examination showed that the head was in the right flank, the left shoulder impacted in the pelvis, breech on the left side and back anterior—R. Ac. D. A. As the shoulder could not be lifted out of the pelvis and the uterus was almost tetanically contracted, it was determined to admit the patient to the hospital.

She was given morphin gr.  $\frac{1}{4}$  hypodermically before the arrival of the ambulance at 10.30 p. m. During the trip to the hospital the pains were very severe, and upon arriving at the front door the patient stated that she thought the child was being born. She was accordingly rushed to the examining room, when examina-

tion showed that the left arm and shoulder and both buttocks were protruding from the vulva, the latter occupying its posterior part. Immediately afterwards the breech descended in the frank position and was followed by both legs and feet, which came down behind the left arm and shoulder, the right arm and shoulder being still within the birth canal. These were rapidly extruded, the head being born last. The placenta followed spontaneously within a few minutes.

The child was dead and unusually limp, but showed no signs of maceration. It weighed 2690 gm., was 50 cm. long and presented the following head measurements: 12.5, 11.5, 10.8, 8.75 and 7 cm. The left arm was swollen and purplish in color, while an oval area 8 x 12 cm., with the left shoulder as a center, presented a similar discoloration, and was in marked contrast to the rest of the surface of the child. This represented the portion which had first become engaged and later had protruded from the vulva.

The child was then taken to the laboratory and it was found that its neck was unusually long and pliable. When placed in a normal pelvis it could be forced through it by exactly the same mechanism as had been observed at the time of labor, thus affording positive evidence that the child had been born by spontaneous evolution by Douglas' mechanism. Numerous photographs were taken, from which the accompanying pictures were drawn.

At the time of admission the patient had a temperature of 100.4° F. and a pulse of 100. Both remained more or less elevated for the first 13 days of the puerperium, the highest temperature being 102° and the highest pulse 120. On the afternoon of the fifth day without any warning, the patient had a hæmorrhage. When seen a few minutes later she had lost about 500 cc. of blood. The fundus was large and boggy and reached to the level of the umbilicus. Massage and ergot by the mouth failed to control the bleeding. On internal examination the cervix was found to be patulous and the finger introduced through it detected a small tag of placental tissue adherent to the anterior wall and fundus. Upon removal it was found to measure 2 x 2.5 cm. The uterus then contracted well, and the bleeding ceased—the total amount of blood lost being approximately 700 cc.

The patient was discharged on the 17th day in good condition with the following findings: Outlet moderately relaxed; cervix, slight tear on left side; uterus forwards, movable, well involuted; slight thickening of the left broad ligament.

CASE II.—*Spontaneous Evolution from L. Ac. D. P. N. J.*, House No. 6736. July 27, 1914. A 26-year-old colored woman, who had had a spontaneous labor four years before. Last menstrual period December, 1913. Pelvis generally contracted; measurements 24, 27, 30, 18, 9.5 cm. Pubic arch narrow; tubers. 8.5 cm.

The patient was registered in the out-patient department (No. 6514) but when labor began, sent for a colored physician, who later called another physician in consultation. After repeated examinations a diagnosis of shoulder presentation was made, and it was requested that the patient be admitted to the hospital.

She was seen by the out-patient obstetrician at 7.40 p. m., when it was learned that labor had begun at 5 p. m. of the previous day and that the membranes had ruptured about 4.30 p. m. this afternoon (July 27). The patient was in bed, very restless and had a temperature of 102.4° F. Palpation showed the fundus four fingers below the xiphoid, the uterus tetanically contracted with the contraction ring running horizontally just about the symphysis. Several subserous myomatous nodules were palpable, and the round ligaments were parallel, but not greatly hypertrophied. Palpation was unsatisfactory, but the fourth maneuver showed that the presenting part was soft and compressible. The foetal heart was not heard, but the mother stated that she had felt distinct movements during the morning.

The pains were of great intensity and occurred every three



minutes, with scarcely any interval between them. The left arm was protruding from the vulva, with the palmar surface of the hand directed upward and toward the right thigh of the patient. When the vulva was spread apart, the left axilla and a portion of the thorax could be seen. Rectal examination showed that the pelvis was filled with the body of the child, whose back was directed to the left and posteriorly. Consequently, a diagnosis of left acromio-dorso-posterior position was made. There was no bulging of the perineum and the patient was given a quarter of a grain of morphin by the mouth and prepared for transportation to the hospital.

At 8.10 p. m. the vulva gaped and the perineum bulged distinctly. As spontaneous evolution was evidently in progress, it was felt advisable to defer the transfer of the patient until later. The arm and shoulder continued to advance and ten minutes later the back of the child came into view and was born sharply bent upon itself until the buttocks reached the perineum. The back of the child having been raised, the buttocks and legs escaped. Slight traction downward brought the occiput under the symphysis, and the head was readily delivered by elevating the body of the child. The right hand was born in extension along the side of the head. The placenta was expelled spontaneously immediately afterwards. There was practically no bleeding during or after the third stage, but two drams of ergotol were given by the mouth prophylactically. Except for the elevated temperature, the patient was left in good condition.

The child was dead, but not macerated. Owing to an unfortunate misunderstanding its body was not sent to the hospital. It weighed 2500 gm. and was 45 cm. long. Its neck was markedly elongated on the left side, and on stretching the arm the distance between the mastoid and the acromion was found to measure nearly 9 cm. The arm was swollen and bluish in appearance and with the scapula formed the center of a "caput succedaneum" 1 to 2 cm. thick. This was bluish and œdematous and involved an area, roughly speaking, 6 cm. in diameter, extending from the left breast to the mid-back, and from the left side of the neck midway to the iliac crests.

Following delivery the patient continued to have fever and an elevated pulse, more or less abdominal pain, and difficulty on micturition. A diagnosis of pyelo-nephritis and localized pelvic peritonitis was made and she was admitted to the hospital on the 12th day after delivery. At that time the following findings were noted: Outlet somewhat relaxed; no sign of fistula; cervix almost flush with vaginal vault, deep bilateral laceration; uterus forwards, slightly enlarged, drawn somewhat to the left side and firmly fixed; adnexa not felt, but on both sides there was an area of induration involving the fornix and posterior vaginal wall which appeared to constrict the rectum. The urine contained a considerable quantity of albumin, some red cells and leucocytes, epithelial cells and a few granular casts. Wassermann negative.

The patient gradually improved on conservative treatment and left the hospital in good condition.

These two cases are of interest for several reasons. Firstly, on account of their rarity, as they are the only examples of birth by spontaneous evolution observed in 13,000 consecutive labors in the Obstetrical Department of The Johns Hopkins Hospital. Secondly, they show that the final stages of the process may be completed with great rapidity, the first child having been born practically in the ambulance, while the second was expelled so rapidly that the patient could not be transported to the hospital. Furthermore, the first case shows that the entire duration of labor may be relatively short, being only eight hours.

Finally, the first case is of particular interest from the fact

that it was possible in the laboratory to force the child through a normal pelvis by a mechanism identical with that observed at the bedside, and to photograph its various stages. From these photographs Mr. Max Broedel was kind enough to prepare the drawings which accompany the article, and which graphically illustrate the main steps in the mechanism.

Fig. 1, which shows the first stage of spontaneous evolution—namely, the impaction of the shoulder into the pelvis, together with the molding and transverse compression of the foetus—does not belong in this series; but is nevertheless strictly accurate, as it was drawn from a foetus contained in a uterus which had been removed at full term on account of atresia of the cervix and profound intra-partum infection, the child being already dead. The entire specimen was hardened in formalin, after a window had been cut in the uterine wall, and was not opened for some weeks, so that the postural relations were accurately preserved.

Fig. 2 shows the condition of affairs after the arm had prolapsed through the vulva. Note the molding of the entire foetus, the attitude of the head, the elongation of the neck, and the swelling and discoloration of the prolapsed arm. This last condition seems to afford indubitable evidence that foetal death had occurred comparatively late in labor and after the arm had prolapsed.

Fig. 3 is of unusual interest, as it represents the crucial stage in the mechanism, and shows conditions which are particularly difficult to explain. In the first place, note that the occiput has rotated almost directly anteriorly and lies just above the right horizontal ramus of the pubis and the symphysis; while the neck is in contact with the inner surface of the symphysis, and has become so stretched and elongated as to permit the left shoulder to emerge beneath the pubic arch. At the same time the buttocks are seen to have emerged from the outlet with their anterior surface in contact with the inner surface of the prolapsed arm. The position of the buttocks is very unusual, is particularly difficult of explanation, and seriously complicates the classification of the mechanism, as will be indicated later. It can be explained only by assuming that, after the left shoulder had emerged beneath the pubic arch, the buttocks had been forced down between the thorax and the posterior pelvic wall, so that they eventually emerged behind the prolapsed arm. It is apparent that such a maneuver must have necessitated great compression and an extreme degree of torsion of the body, which could scarcely be compatible with the life of the child. Consequently, it is permissible to assume that foetal death must inevitably have taken place at that time, if it had not occurred previously.

Fig. 4 shows that after delivery of the shoulder and buttocks the child had undergone a movement of rotation, by which the prolapsed arm returned to the side of the mother toward which it was originally directed, thus bringing the occiput under the pubic arch in the most suitable position for easy expulsion.

In the second case the evolution was clearly effected by the mechanism described by Douglas, but it is not so easy to explain which mechanism was concerned in the first case.



Before attempting to do so, I shall refer to the histological aspects of the subject, as only in that way will it be possible to find one's way among the contradictory statements which have been made concerning the mechanisms of Denman and Douglas and the relative frequency with which they occur.

As has already been indicated, the term spontaneous evolution was introduced by Sir Thomas Denman in the latter part of the 18th century, and the first reference to it which I have been able to find is in an article in the *London Medical Journal* for 1785, entitled "Observations to prove that in cases where the upper extremities present, at the time of birth, the delivery may be effected by the spontaneous evolution of the child." In this article Denman reported three personal cases, and stated that including these some thirty cases had been observed. I shall quote his first case verbatim:

CASE I.—In the year 1772 I was called to a poor woman in Oxford street, who had been in labor all the preceding night, under the care of a midwife. Mr. Kingston, now living in Charlotte street, and Mr. Goodwin, surgeon at Wirksworth, in Derbyshire, who were at that time students in midwifery, had been sent for some hours before I was called. The arm of the child presenting, they attempted to turn and extract it by the feet, but the pains were so strong as to prevent the introduction of the hand into the uterus. I found the arm much swelled and pushed through the external parts in such a manner that the shoulders nearly reached the perineum. The woman struggled vehemently with her pains, and during their continuance I perceived the shoulder of the child to descend. Concluding that the child was small and would pass doubled, through the pelvis, I desired one of the gentlemen to sit down to receive it, but the friends of the woman would not permit me to move. I remained by the bedside till the child was expelled, and I was very much surprised to find that the breech and inferior extremities were expelled before the head, as if the case had originally been a presentation of the inferior extremities. The child was dead, but the mother recovered as soon and as well as she should have done after the most natural labor.

The essentials of the other cases are contained in the following quotations: Case II: "No further attempts were made to turn the child. Then every pain propelled it lower into the pelvis, and in a little more than one hour the child was born, the breech being expelled as in the first case." Case III: "On examination the arm pushed through the external parts, the shoulder pressing firmly upon the perineum. The exertions of the mother were wonderfully strong. I sat down while she had two pains, by the latter of which the child was doubled and the breech expelled. I extracted the shoulders and head and left the child in bed." From these descriptions it is impossible to learn exactly what occurred, except that the children had been born spontaneously, and that the breech had been expelled before the head.

Moreover, it is apparent that Denman was not quite certain himself, as is clearly shown by the following statement at the end of the article:

Though knowledge of the fact has already been attended with advantages to many women in very deplorable circumstances, much remains to be done to complete the doctrine, not by reasoning upon the subject, but by careful attention to practice.

As far as I can ascertain his first attempt to describe the mechanism was in a letter written to Douglas just after the

appearance in 1811 of the first edition of his pamphlet, "The Explanation of the Real Process of the Spontaneous Evolution of the Foetus," from which the following quotation is taken:

As to the manner in which this evolution takes place, I presume that after the long continued action of the uterus, the body of the child is brought into such a compact state as to receive the full force of every returning action. The body in its doubled state, being too large to pass through the pelvis, and the uterus pressing upon its inferior extremities, which are the only parts capable of being moved, they are forced gradually lower, making room, as they are pressed down, for the reception of some other part into the cavity of the uterus which they have evacuated, until the body, turning as it were upon its own axis, the breech of the child is expelled, as in an original presentation of that part; nor has there been anything uncommon in the size and form of the pelvis of these women, to whom this case has happened, nor have the children been small or softened by putrefaction.

Douglas, in the second edition of his monograph which appeared in 1819, took issue with Denman, and stated that while spontaneous evolution undoubtedly occurred it was effected by an entirely different mechanism. This opinion was based upon his personal observation of seven cases, in all of which the arm and shoulder of the child emerged from the vulva before the rest of the body; and this being the case he contended that it was impossible for the breech to be born first. He described as follows the situation of the foetus immediately prior to its expulsion:

The entire of it somewhat resembles the larger segment of a circle; the head rests on the pubis internally; the clavicle presses against the pubis externally, with the acromion stretching towards the mons veneris; the arm and shoulder are entirely protruded, with one side of the thorax not only appearing at the os externum (vulva), but partly without it; the lower part of the same side of the trunk presses on the perineum, with the breech either in the hollow of the sacrum or at the brim of the pelvis, ready to descend into it; and by a few uterine efforts the remainder of the trunk, with the lower extremities, is expelled. And to be still more minutely explanatory in this ultimate stage of the process, I have to state that the breech is not expelled sideways, as the upper part of the trunk had previously been; for during the presence of that pain, by which the evolution is completed, there is a twist made, about the center of the curve, at the lumbar vertebræ, when both buttocks, instead of the side of one of them, are thrown against the perineum, distending it very much; and immediately after the breech, with the lower extremities, issues forth, the upper and back part of it appearing first, as if the back of the child had originally formed the convex and its front the concave side of the curve.

So convincing was Douglas' exposition, that Walter Channing, in an appendix to his American edition of Denman's *Aphorisms*, stated that Denman's interpretation of the process was incorrect; and still further support was lent to this doctrine by the contributions of Dubois. This view obtained immediate acceptance among English and French writers, and Tarnier and Chautreuil, Ribemont-Dessaignes and Lepage, Puech and Lequeux, Rouvier and other French writers describe Douglas' mechanism as the only one obtaining in spontaneous evolution. Indeed, Puech and Lequeux state that Denman's mechanism does not occur, and that the cases which have been described as such are really examples of spontaneous evolution.





FIG. 1.



FIG. 3.



FIG. 2.



FIG. 4.







On the other hand, German authorities have clung to Denman's explanation, which was the only one mentioned by Küstner in Müller's *Handbuch der Geburtshilfe*. Von Franque and Zangemeister, who have recently written extensively upon the subject, hold that spontaneous evolution may be effected by either the Douglas or the Denman mechanism, but that the latter is comparatively infrequent. Thus, of 55 cases collected by Zangemeister, in which full details of the process were available, in only 12 was the delivery by Denman's mechanism; and several of these were doubtful.

Furthermore, when one studies the detailed description of the latter, as given by Zangemeister, it becomes apparent that it differs in many respects from the process described by Denman. According to Zangemeister, this mechanism usually occurs in dorso-posterior positions, and can be effected only by the buttocks being pushed past the impacted shoulder. As the buttocks descend, the shoulder gradually rises out of the pelvis and draws up the arm with it. At the same time, the head, instead of rotating anteriorly, moves posteriorly and eventually comes to lie over one of the sacro-iliac joints in front of the promontory. In this event the shoulder is not the first part of the child to emerge from the vulva, but rather the lower abdomen or the buttocks. After the breech has been expelled, the abdomen, thorax, shoulders and head successively emerge.

That almost fully developed children may be delivered by such a mechanism must be admitted, as it is vouched for by Zangemeister and other competent German authorities. But I contend that it is scarcely justifiable to describe it as Denman's mechanism. In the first place it does not correspond with Denman's theoretical explanation, which called for a rotation of the foetus about its long axis, and in the second place, it does not tally with Denman's description of the course of labor in his Case I, in which he "perceived the shoulder of the child to descend." Furthermore, he did not claim that the breech was expelled before the anterior shoulder, but merely reported that "he was very much surprised to find that the breech and inferior extremities were expelled before the head." As this likewise happens when the child is born by the Douglas mechanism, it seems gratuitous to assume that it was expelled in any other way.

For these reasons it appears to me to be inexpedient to con-

tinue to speak of a Denman mechanism, more particularly as careful study of a number of the reported cases makes it quite possible that the respective authors were mistaken as to what had actually occurred.

Reverting once more to my first case, it seems to me to be unjustifiable to describe it as an example of spontaneous evolution by Denman's mechanism, for the reason that the arm and shoulder were born before the breech. Consequently, it would appear best to classify it as an instance of an abnormal or complicated Douglas' mechanism.

I am perfectly conscious that what I have put forward has contributed but little to our knowledge, but if it leads to increased interest in the subject of spontaneous evolution, I shall feel amply repaid for my trouble in preparing this article.

In conclusion, I desire to express my thanks to my former chief, Dr. J. Whitridge Williams, for permission to publish the cases, and for many suggestions in the preparation of this article.

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## NOTES ON NEW BOOKS.

*The Brain in Health and Disease*: By JOSEPH SHAW BOLTON, M. D., D. Sc., F. R. C. P. (Lond.). (New York: Longmans, Green & Co.)

In the introduction the reader is warned that the work must not in any sense be considered a text-book on mental disease, but that it should rather be looked upon as in the nature of a treatise on general cerebral physiology and pathology. The work is really based on original researches of the author carried on during the past eighteen years, and it gives ample proof of laborious, painstaking, and in some ways very interesting efforts. It is divided into two parts dealing with cerebral function in the normal and in the insane brain, respectively. The latter portion is subdivided

into sections dealing with cerebral function in the sub-normal or sub-evolved brain (amentia), and in the involuted or dissolved brain (dementia). Under these two headings of Amentia and Dementia all mental diseases are classified.

In considering the general histology of the cerebral cortex the author's method of micrometric measurement of the primary cell and fiber-laminae is fully described and it is very interesting, but he gets quite out of his depth when he attempts to draw clinical correlations. His method of examination consists in measuring accurately vertical sections from four regions of the convolutions, and then from these a general average measurement is obtained. The regions recommended are the *flat surfaces* or external parts



between fissure lips, the *apices* or fissure lips, the *bottoms* of fissures, and the *sides* of fissures at some point between the apices or fissure lips and the bottom of the fissures. This method of examination is no doubt a very ingenious one, but after his results have all been recorded and summarized, the following final remark is added: "I would add that there is reason to believe that this physical basis of the cerebral functions, which exhibits such well-marked variations in the subjects of mental alienation, exhibits equally important though less extensive variations in the case of presumably normal individuals."

In reference to the above remark it must be noted that no guides are given so as to enable one to say when the normal ceases and when the abnormal begins. Furthermore, when one finds such conditions as hysteria, paranoia, and recurrent insanity classified as states of sub-evolution or amentia, one is inclined to question the author's clinical experience. If he had confined himself to a description of the histo-pathology of the cerebral cortex, and had not attempted to draw clinical deductions, it would have been a pleasure to congratulate him on his work, but his clinical observations are so confused and so little analyzed that for students the book would be most misleading.

D. K. H.

*Pharmacology, Clinical and Experimental.* By HANS H. MEYER and R. GOTTLIEB. Authorized English translation by JOHN TAYLOR HALSEY. Price, \$6.00. (Philadelphia: J. B. Lippincott Company, 1914.)

This book is the result of years of work and thought along the lines of pharmacology on the part of two leading European pharmacologists. It can be read with profit by every up-to-date scientific man of medicine. It has a peculiar value for the teacher of medicine.

Whereas most books on the subject begin with a consideration of drugs, this one starts each chapter with a description of an organ or system of organs together with functional considerations and the mechanism normally involved. The reader is thus oriented anatomically and physiologically. The influence of each drug concerned is then brought into relation in such a way that the reader obtains an unusually clear picture of its pharmacological action. This arrangement of material is excellent. Diagrams enhance the value of the work.

The translation is good and Dr. Halsey has added many valuable remarks and suggestions.

L. G. R.

*Nervous and Mental Diseases.* By ARCHIBALD CHURCH, M. D., Professor of Nervous and Mental Diseases in Northwestern University Medical School, Chicago; and FREDERICK PETERSON, M. D., formerly Professor of Psychiatry, Columbia University. Eighth edition, revised. Octavo volume of 940 pages, with 350 illustrations. Cloth, \$5.00 net; half Morocco, \$6.50 net. (Philadelphia and London: W. B. Saunders Company, 1914.)

In the eighth edition the section devoted to nervous diseases has been modified here and there, but on the whole there is comparatively little change in the material. In the preface reference is made to the changes introduced in the paragraphs dealing with syphilis of the nervous system and with investigations of the cerebro-spinal fluid. As a matter of fact no reference is made to Lange's colloidal gold test, and the whole subject is discussed in a very formal and somewhat inadequate manner.

The section on mental diseases does not attempt to discuss broad psychiatric issues, but consists of a rather formal classification of the psychoses with a detailed description of well-known text-book entities.

The book is not calculated to stimulate the interest of the medical student in mental diseases.

C. M. C.

*Burdett's Hospitals and Charities. 1915. Being the Year Book of Philanthropy and the Hospital Annual.* By SIR HENRY BURDETT, K. C. B., K. C. V. O. Twenty-sixth year. (London: The Scientific Press, Limited, 1915.)

The above volume has made its appearance with commendable punctuality notwithstanding the delay which might have been expected in consequence of the unsettled state of affairs in Europe.

The book itself contains the usual information which has been so valuable to all hospital administrators during the past 25 years. The only feature of value before us which requires special mention is a new chapter on the "Future Outlook and the Extension of Voluntary Hospitals." This is an interesting chapter because it contains a plea for bringing the voluntary hospitals, or as we would say in this country the corporate hospitals, of England more into accord with the methods which exist in the United States. It is evident that the editor, Sir Henry Burdett, is a man of strong political bias, as shown by his arraignment again and again of the politicians who procured the passage of the National Insurance Act. He charges that they do great damage to voluntary hospitals by ignoring the fact that insured persons when seriously ill require hospital treatment; and consequently making no provision for it. He believes that this has brought a severe burden upon the managers of these hospitals, which have been crowded by insured persons to the exclusion of the industrial class, who are not insured. He declares that if the example of Germany and other foreign countries had been followed, where adequate hospital treatment for insured persons is supplied in connection with such insurance, at least 50,000 additional beds ought to have been provided in the hospitals of the United Kingdom. But nothing has been done.

It is also asserted that at the present time all voluntary hospitals have a twofold demand made upon them, arising out of the necessity to care for wounded soldiers, and to carry out the provisions of the National Insurance Act, both of which tend to crowd them to the exclusion of indigent persons for whom the hospitals were originally created.

In the opinion of the accomplished editor the only remedy to prevent a deficiency in funds for the support of voluntary hospitals is to be found in the reception and treatment of paying cases who are able to make an adequate compensation for their care and treatment, and also for persons in less comfortable circumstances who are not insured but who are able to pay some portion of the cost of treatment. He cites the example of the United States to show how much can be done to help voluntary hospitals in this way.

He states very forcibly that voluntary hospitals have a strong hold upon the minds of the well-to-do class, who appreciate their efficiency and what they have done for medical science, and who are looking for opportunities for personal service. In his judgment they are a valuable asset to the community and should be fostered in every way.

Under the chapter entitled "British Hospital Progress" he notes the tendency to establish in connection with general hospitals separate wards for the treatment of venereal diseases, and believes that the effect has been to lessen the amount of suffering from them, and to safeguard the community.

The loss of surgical attendants and members of the nursing staff in voluntary hospitals in consequence of the war is deplored, and fears are expressed that it may be difficult to ask from the hospitals the proper care of sick and wounded soldiers, and at the same time secure care and treatment of the sick poor from them.

The tribute to the voluntary hospital on page 102 is worthy of being cited here:

"The voluntary hospital from the moment it became a great center of education—scientific, technical, moral, mechanical, and



personal—has as a necessary consequence increased yearly in value as a storehouse and center of knowledge. Who can estimate, nay, who can exaggerate, the value to the race and to humanity everywhere of the knowledge gathered up by experience and practised in a great modern hospital for the sick? All this knowledge and every addition made to it is transmitted through able teachers—some of the greatest and most proficient scientists and the most devoted and skilled members of the nursing profession—to those who, when equipped with knowledge and depth in the practice of their profession by the skill they have acquired in the hospital, go forth into the world to carry on the beneficent work amongst all who may fall out on life's journey when struck down by sickness or overtaken by accident. To-day the knowledge garnered and preserved in the hospital storehouse is systematized and reduced to order upon a carefully thought-out plan, which makes it readily available for use at all times, not only by members of the present generation, but for those who are to follow."

A marked feature of the book is the insistent demand which he makes that the Government shall come to the assistance of these hospitals by freeing them from taxation, by providing duty-free alcohol, and by calling upon all philanthropists to assist them.

The volume contains its former valuable statistics.

It is to be hoped that the time will come when a similar publication can find a field in the United States.

During the 26 years of publication this annual has done much to unify hospital methods and to increase interest in hospitals throughout the world.

H. M. H.

*Biochemic Drug Assay Methods. With Special Reference to the Pharmacodynamic Standardization of Drugs.* By PAUL S. PITTENGER, PH. G., PH. C., PHAR. D. Edited by F. E. STEWART, M. D., PH. G. Cloth, \$1.50. (Philadelphia: P. Blakiston's Son & Co., 1914.)

This small volume of 140 pages describes in considerable detail the most frequently used methods of biochemically standardizing drugs. It is elementary in character, well illustrated and gives the formulæ of various solutions employed. It deals with the standardization of cardiac stimulants and depressants, epinephrin and products of the suprarenal glands, ergot, pituitary extract and cannabis indica. A fairly complete bibliography is attached.

Attention might be called to a typographical error. Locke's solution is referred to as Loche's solution. The book will prove of decided value to pharmacologists and therapeutists.

L. G. R.

*Modern Medicine: Its Theory and Practice.* Edited by SIR WILLIAM OSLER, BART., M. D., F. R. S., and THOMAS MCCRAE, M. D. Second edition. Vol. II. Diseases caused by Protozoa and Animal Parasites; Diseases due to Physical, Chemical and Organic Agents; Diseases of Metabolism and of the Respiratory System. (Philadelphia: Lea & Febiger, 1914.)

The titles covered by this volume indicate its importance. The general field of protozoology has been included in medicine, in which so much change is taking place.

The names of Richard Strong, Charles Craig Stephens, Sir David Bruce, John Todd, are a guarantee that the articles are up to date and authoritative.

Part II contains Dr. Stiles' brief résumé of human (metazoan) parasites, which is the only publication of the kind in the English language that is reasonably complete. This section alone is worth the price of the volume.

It is interesting to note the change in the notice given pellagra in the two editions. In the first edition (1907) it was accorded a paragraph of ten lines under food poisons. The new edition contains an admirable article by Beall, consisting of 17 pages with two good plates.

Altogether, the second volume is fulfilling admirably the promise of improvement in format, page, illustration and binding, and the subject-matter is hard to equal in any system.

T. R. B.

*Pathogenic Microorganisms.* By WILLIAM HALLOCK PARK, M. D., Professor of Bacteriology and Hygiene, University and Bellevue Hospital Medical College, and Director of the Bureau of Laboratories of the Department of Health, New York City; and ANNA W. WILLIAMS, M. D., Assistant Director of the Bureau of Laboratories, Consulting Pathologist to the New York Infirmary for Women and Children. Fifth edition. Cloth, \$4.00. (Philadelphia: Lea & Febiger, 1914.)

This book has undergone a most interesting evolution. The first edition, called "Bacteriology of Medicine and Surgery," published by Park, was intended almost entirely for medical practitioners. The subsequent editions have been gradually made more comprehensive until the present, which must rank not only as a most valuable reference work for the use of physicians but also as one of the best text-books of bacteriology for the student's use.

In the present edition there is an advantageous rearrangement of the subject-matter, a thorough revision of many of the chapters and a new chapter on filtrable viruses. But most important is the fact that all of the very latest work has been judiciously criticised and incorporated in the text. The illustrations are splendid; the bibliography, although incomplete, will prove of material assistance to the reader. In fine, it may be said that the value of the book for physicians, students and laboratory workers is permanently established.

M. C. W.

*Pyelography.* By WILLIAM F. BRAASCH, M. D. Cloth, \$5.00. (Philadelphia: W. B. Saunders Company, 1915.)

The author is to be congratulated upon the very valuable work which he has presented to the medical profession. With the wealth of material at his command, he has been able to cover the subject from every conceivable standpoint.

His subject has been treated exclusively from an X-ray standpoint, and what can be deduced from this method of examination. It has been treated systematically, and practically every variation of the renal pelvis, whether anatomical or pathological, has been taken up.

It is very difficult indeed to pick out any distinctive chapter, as the subject-matter throughout is so good that no one part stands out more than the other. Mention, however, must be made of the chapter on the normal pelvis. All the variations that are to be found in a normal pelvis have been taken up. Each has been so thoroughly described and illustrated that one gets an absolutely clear conception of the subject. To anyone who is familiar with this type of work, the value of these illustrations is apparent at once, as so frequently the question arises as to whether we are dealing with a variation of a normal pelvis or the beginning of a pathological condition.

Then, too, his chapter on technique is to be especially commended, as it describes so thoroughly the proper method for making this examination. The importance of this point can hardly be insisted upon too strongly, in view of the fact that in the hands of a beginner the injection of the pelvis of the kidney is sometimes done in a careless and haphazard manner, which not only fails to give results, but also is actually dangerous to the patient.

After the chapter on technique and the normal pelvis, Braasch takes up successively the abnormal positions of the kidneys, the mechanical dilatations, the inflammatory dilatations, calculi, renal tumors and congenital anomalies. Each subdivision, however, is described and illustrated.



In conclusion, it may be said that the book is of great value from two standpoints: first, it contains a very excellent description of the various conditions; and secondly, it presents a great number of very excellent illustrations, which puts it almost in the class of an atlas.

F. H. B.

*Radiography, X-Ray Therapeutics and Radium Therapy.* By ROBERT KNOX, M. D. Cloth, \$8.00 (New York: Macmillan Company, 1915.)

In the preface the author states that the object of this work is to present to the student and practitioner, in as concise and practical form as possible, the essential points in radiography, X-ray therapeutics and radium therapy. Reading the book from this standpoint, one can say that he has fulfilled his obligations.

It is perfectly true that in radiology one must have quite an understanding of the mechanics for the production of radiograms. Unfortunately, in the section of the book treating of radiology alone, a third of it is given up to the description of apparatus. Another third is devoted to the method of examination. The remaining third is made up largely of illustrations, with the briefest kind of description of the pathological conditions. This is rather unfortunate, as by far the most difficult thing in radiology is the interpretation of the radiograms. The mechanical part is easily mastered and, in fact, can be done by a skilled technician, but the real value of radiology lies in the proper interpretation of the findings; and it certainly would seem that, if less space were devoted to the technical part and more to what might be termed the truly medical part, a text-book would be of much more value, not only to the beginner, but even to the skilled radiologist.

As an instance of the brevity with which the various subjects are treated, the gastro-intestinal tract, as regards not only the normal but also the pathological conditions, is dealt with in about twelve pages. The section on therapy is short, but quite good. The final section of the book is devoted to radium therapy, and includes a discussion of the physics and the application of radium.

F. H. B.

*Diagnostic and Therapeutic Technique.* A manual of practical procedures employed in diagnosis and treatment. By ALBERT S. MORROW, M. D. Second edition. Cloth, \$5.00. (Philadelphia and London: W. B. Saunders Company, 1915.)

This volume, of over 800 pages, covers a wide range of diagnostic and therapeutic measures, and includes practically everything that a general practitioner of medicine would be justified in attempting without the help of a skilled surgeon or specialist. In fact several procedures are included, such as direct arterio-venous anastomosis, which would better have been reserved exclusively for men with special training and experience. Aside from the ordinary simpler procedures, considerable space is devoted to anesthesia, local and general; to cystoscopy, and ureteral catheterization; to the instrumental treatment of strictures; to the simpler methods of examining the nose and sinuses, the pharynx, and larynx; and to the use of the bronchoscope and proctoscope.

In general the directions are brief, but clear and explicit, and are amplified by numerous illustrations. An attempt is made to indicate briefly the practical application of the methods outlined, and the dangers in, or contraindications to, their use.

As is inevitable, there are errors of omission, and statements to which exception may be taken. Thus, in discussing methods for the direct transfusion of blood, the use of syringes, the only method a man of ordinary training could hope to master, is discarded for the very difficult vessel-to-vessel method. Further, the outline of the dangers of agglutination or hæmolysis following

the use of blood from unsuitable donors is very incomplete, and even misleading. The dangers of lumbar puncture, and particularly of intra-meningeal injections, where a syringe is used and the pressure exerted not accurately controlled, are not sufficiently emphasized.

On the whole, however, the book is a commendable one. It is not intended for the specialist, but should meet the demands of the student and general practitioner.

P. W. C.

*Medical Ethnology.* By CHARLES E. WOODRUFF, A. M., M. D., Lieutenant-Colonel, U. S. Army Medical Corps (Retired). (New York: Rebman Company, 1915.)

The author explains in his preface that this work was begun as a revision of the first edition of his "Effects of Tropical Light on White Men," a book which some years ago attracted widespread and well-deserved attention, but that the title was changed to "Medical Ethnology" because of the development of our knowledge that many other factors besides pigmentation enter into the causation of the differences between the races and sub-races of men. It is a matter of congratulation to students of ethnology that this change of plan was made, as it has given the author an opportunity to present a mass of valuable data from his own experience in various parts of the world and the results of a wider study of the literature.

Medical ethnology may be briefly defined as the science which deals with the morbidity of races and the changes of types which result from their physical and mental reaction to their environment. Changes in type, the author asserts, are going on constantly, and the characteristics, tendencies and future of any given race cannot be explained or predicted without a full knowledge of its environment. Heredity is defined as an "organic inertia" of the individual or race and is in fact the inability of a person or species to modify itself to environment when placed among new surroundings. Such organic inertia explains also the reason why many races die out when transferred to unfavorable climates, or when called upon to meet conditions of life for which they are physically unfit. The type of the race sooner or later is produced by its environment.

The whole book is made up of the development of these ideas. It is full of interest, but unfortunately it does not lend itself to a brief summary and needs to be read from cover to cover. The effects of ether waves, infra-red and ultra-violet rays, X-rays and radium, are given in considerable detail to explain the effect of light upon growth and development. Unless races are able to adjust themselves to light and heat by protective pigmentation, they degenerate. Survival of migrants depends upon this and also upon physical characters such as the size and shape of the air passages and the openness of the nostrils. The effects of pigmentation, congenital or acquired, and the reaction of the nervous and physical systems to light should not be forgotten. Contrary to the opinion of medical men generally, the author believes that too much sunlight is injurious to all but the deeply pigmented races.

The chapters entitled "Causes of Extinction," "Ethnic Psychology" and "Practical Application of Medical Ethnology" are especially valuable. The book is the fruit of much thought and wide research.

The above imperfect and inadequate note had scarcely been written, when news came of the death of the accomplished author. All who knew him and were interested in his contributions to the science of race development and decay can but join in the heartfelt but unavailing regret that his life was not spared to complete his studies. It is evident that he had not reached final conclusions and was still gathering material for further deductions. A laborious and painstaking investigator like Colonel Woodruff is rare indeed in the ranks of the medical profession!

H.



*Principles of Hygiene.* By D. H. BERGEY, A. M., M. D. Cloth, \$3.00. (Philadelphia: W. B. Saunders Company, 1915.)

The fifth edition of Bergey's *Principles of Hygiene* deserves more than a word of commendation. The form and size of the earlier editions are retained, and to a large extent the clearness and simplicity which mark the presentation of the subject-matter. The general literature of hygiene has evidently been closely followed by the author, and this has made itself felt in certain chapters. Particularly should be mentioned the chapter on Food and Dieting, in which excellent tables illustrative of the caloric

values of different articles of diet are to be found, and other tables giving an accurate comparison of caloric values and the cost of nearly all our foods. The subject of Industrial Hygiene is ably presented in a rather short chapter of less than 20 pages, and School Hygiene in a somewhat similarly brief but thorough manner. The sections on Military Hygiene and Naval Hygiene are of particular interest in the present world crisis. Finally, especial mention should be made of the chapter on Vital Causes of Disease, in which the important epidemiological factors relating to the ordinary infections are clearly brought out.

W. W. F.

## BOOKS RECEIVED.

*Public Health Reports.* Issued weekly by the United States Public Health Service. Containing Information of the Current Prevalence of Disease, the Occurrence of Epidemics, Sanitary Legislation, and Related Subjects. Vol. XXIX, Part I, Nos. 1-26, January-June, 1914. 1915. 8°. 1752 pages. Government Printing Office, Washington.

*Southwestern Medical and Surgical Association.* Transactions of the First Annual Session of the Southwestern Medical and Surgical Association. C. F. Braden, editor. 1914. 4°. 156 pages. El Paso, Texas.

*The Gold-Headed Cane.* By William Macmichael, M. D. With an Introduction by Sir William Osler, B. A., M. D., F. R. S. And a Preface by Francis R. Packard, M. D. 1915. 8°. 261 pages. Paul B. Hoeber, New York.

*Radiography, X-Ray Therapeutics and Radium Therapy.* By Robert Knox, M. D. (Edin.), M. R. C. S. (Eng.), L. R. C. P. (Lond.). With 64 plates, 246 illustrations in the text and a frontispiece in color. 1915. 4°. 406 pages. The Macmillan Company, New York.

*A Reference Handbook of the Medical Sciences.* Embracing the Entire Range of Scientific and Practical Medicine and Allied Science. By various writers. First and second editions edited by Albert H. Buck, M. D. Third edition, completely revised and rewritten. Edited by Thomas Lathrop Stedman, A. M., M. D. Complete in eight volumes. Vol. V. Illustrated by numerous chromolithographs and 733 half-tone and wood engravings. 1915. 923 pages. 4°. William Wood & Co., New York.

*Pyelography (Pyelo-Ureterography).* A Study of the Normal and Pathologic Anatomy of the Renal Pelvis and Ureter. By William F. Braasch, M. D. Containing 296 pyelograms. 1915. 8°. 323 pages. W. B. Saunders Company, Philadelphia and London.

*Pathological Technique.* Including Directions for the Performance of Autopsies and for Clinical Diagnosis by Laboratory Methods. By Frank Burr Mallory, A. M., M. D., and James Homer Wright, A. M., M. D., S. D. Sixth edition, revised and enlarged. With 174 illustrations. 1915. 8°. 536 pages. W. B. Saunders Company, Philadelphia and London.

*The Clinics of John B. Murphy, M. D., at Mercy Hospital, Chicago.* Vol. IV, No. 2, April, 1915. 1915. 8°. W. B. Saunders Company, Philadelphia and London.

*International Clinics.* A Quarterly of Illustrated Clinical Lectures and Especially Prepared Original Articles. By leading members of the medical profession throughout the world. Edited by Henry W. Cattell, A. M., M. D. Vol. II. Twenty-fifth series. 1915. 8°. 312 pages. J. B. Lippincott Company, Philadelphia and London.

*Medical Ethnology.* By Chas. E. Woodruff, A. M., M. D. 1915. 8°. 321 pages. Rebman Company, New York.

*Medical Applied Anatomy.* For Students and Practitioners. By T. B. Johnston, M. B., Ch. B. Containing three full-page plates in color and 146 other illustrations in the text. 1915. 12°. 436 pages. A. and C. Black, Limited, London.

*Progressive Medicine.* A Quarterly Digest of Advances, Discoveries and Improvements in the Medical and Surgical Sciences. Edited by Hobart Amory Hare, M. D., assisted by Leighton F. Appleman, M. D. Vol. II, June, 1915. 1915. 8°. 445 pages. Lea & Febiger, Philadelphia and New York.

*Human Physiology.* By Professor Luigi Luciani. Translated by Frances A. Welby. Vol. I. Circulation and Respiration. 1911. 8°. 592 pages. Vol. II. Internal Secretion; Digestion; Excretion; The Skin. 1913. 8°. 558 pages. Vol. III. Muscular and Nervous Systems. 1915. 8°. 667 pages. Macmillan & Co., Limited, London.

*Stanford University Medical Publications.* Bulletin No. 2, 1913-14. 4°. San Francisco, Cal.

*What Every Mother Should Know about Her Infants and Young Children.* By Charles Gilmore Kerley, M. D. 1915. 12°. 107 pages. Paul B. Hoeber, New York.

*The Clinics of John B. Murphy, M. D., at Mercy Hospital, Chicago.* Vol. IV, No. 1, February, 1915. 1915. 8°. W. B. Saunders Company, Philadelphia and London.

*The Vicious Circles of Neurasthenia and Their Treatment.* By Jamieson B. Hurry, M. A., M. D. (Cantab.). With illustrations. 1915. 8°. 90 pages. J. & A. Churchill, London; P. Blakiston's Son & Co., Philadelphia.

*University of Pennsylvania. Eighth Report of the Henry Phipps Institute for the Study, Treatment, and Prevention of Tuberculosis.* Factors Affecting the Health of Garment Makers. By H. R. M. Landis, M. D., and Janice S. Reed. 1915. 4°. 104 pages. Henry Phipps Institute, Philadelphia.

*American Association for Study and Prevention of Infant Mortality.* Transactions of the Fifth Annual Meeting, Boston, Mass., November 12-14, 1914. 1915. 8°. 391 pages. Franklin Printing Company, Baltimore.

*University of Michigan. Contributions from the Department of Obstetrics and Gynecology.* Vol. III, 1912-1914. 1914. 8°. Ann Arbor, Michigan.

*College of Physicians.* Transactions of the College of Physicians of Philadelphia. Third Series. Vol. XXXVI. 1914. 8°. 388 pages. Philadelphia.

*John Shaw Billings. A Memoir.* By Fielding H. Garrison, M. D. Illustrated. 1915. 8°. 432 pages. G. P. Putnam's Sons, New York and London.



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# BULLETIN

OF

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## IMPORTANT CONTRIBUTIONS TO CLINICAL MEDICINE DURING THE PAST THIRTY YEARS FROM THE STUDY OF HUMAN BLOOD PRESSURE.<sup>1</sup>

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### INTRODUCTION.

Although Vierordt's crude attempts to measure the compressibility of the pulse by the attachment of weights to a sphygmograph were made many years before, the clinical study of blood pressure really dates from the publication by von Basch, in 1881, of work done with his first sphygmomanometer. When this association first met, 30 years ago, interest in the new method was confined to von Basch and his immediate pupils, and neither the transactions of this society nor the standard text-books on practice of the day make the slightest reference to the method or its results. In the sixth edition of Flint's "Practice of Medicine," published in 1886, in the preparation of which Dr. William H. Welch assisted, and which represented the best clinical knowledge of that time, one finds statements such as these:

"A well-recognized form of cardiac hypertrophy is that which is secondary to certain forms of chronic Bright's disease, particularly to the small granular kidneys. The explanation of this is not thoroughly understood. It will be referred to under the head of

Bright's Disease. Suffice it to say here that it is probably due to some resistance to the blood current through the small vessels"; and "As already stated, simple hypertrophy of the left ventricle of the heart may have a causative relation to cerebral hemorrhage by increasing arterial tension." In describing the clinical history of apoplexy he says: "The pulse is usually diminished in frequency, full and hard, the artery striking against the finger like a metal rod."

These quotations show the clear recognition, by the unaided senses of the clinician, of the existence and associations of high blood pressure, but no material advance in its detection or in the study of the problems presented by it since the days of Richard Bright half a century before.

In 1891 an important paper on Bright's disease was presented before this association by Dr. Francis Delafield.<sup>2</sup> In it he speaks frequently of contraction of the arteries and of the disturbance of the circulation, to which he attributes the cerebral symptoms and dropsy of nephritis and for which he advocates drugs which dilate the arteries. The same year a discussion of the relations between arterial disease and visceral

<sup>1</sup>Read at the thirtieth annual meeting of the Association of American Physicians, Washington, May 11, 1915.

<sup>2</sup>Delafield, Francis: On the diseases of the kidneys popularly called Bright's disease. Tran. Assn. Amer. Phys., 1891, VI, 124-154.



changes was led by Drs. Peabody<sup>\*</sup> and Councilman,<sup>†</sup> and participated in by such distinguished clinicians as Drs. Ord and Gairdner, with casual allusions to increased arterial tension and spasm of the arteries, but no reference whatsoever to the existence of any clinical knowledge of blood pressure.

In 1899, Dr. Stengel read a paper upon the immediate and remote effects of athletics upon the heart and circulation, without making any mention of blood pressure, and in the discussion which followed Dr. Meigs made this remarkable statement:

The doctrines that were generally accepted 20 years ago in regard to Bright's disease and the hypertrophy of the heart so commonly associated with it have fallen almost entirely into discredit. We used to be told that kidney disease caused increased resistance within the arteries, and this threw more work upon the heart, which in answer underwent hypertrophy and grew strong. Little is heard of this any more, and Bright's disease is less and less frequently used as a diagnostic term.

The first paper that dealt with blood pressure specifically was the important presentation at the twelfth meeting, in 1897, by Abel and Crawford, of the isolation of chemically pure epinephrin.<sup>‡</sup> This was, however, experimental work.

The first report of observations on human blood pressure was made in 1903 by Dr. Richard C. Cabot, as part of a paper describing "Studies on the Action of Alcohol in Disease, Especially upon the Circulation." This was a careful clinical study of a therapeutic problem in 58 cases, the Riva-Rocci sphygmomanometer and the original Oliver hemodynamometer being the instruments employed.

At the meeting in 1904 another paper by Dr. Cabot<sup>\*</sup> dealt altogether with blood pressure measurements, and two by Dr. Stengel<sup>†</sup> contained studies on arterial pressure. One of these<sup>‡</sup> was in collaboration with the late Dr. W. B. Stanton, who played an important part in securing the adoption of the sphygmomanometer by the American practitioner as part of his armamentarium.

From the year 1906, when the association so kindly endured my maiden presentation on hypertension, to the present time, no meeting has been without several papers on blood pressure problems, clinical or experimental, and for the past seven years all have shown that clinical blood pressure measurements have become a permanent part of the routine examination of the circulatory system.

In 1886 the literature of human arterial pressure, so far as I have been able to collect it, comprised twelve titles. It is

<sup>\*</sup> Peabody, George L.: Relations between arterial disease and visceral changes. *Trans. Assn. Amer. Phys.*, 1891, VI, 154-178.

<sup>†</sup> Councilman, William T.: On the relations between arterial disease and tissue changes. *Ibid.*, 179-192.

<sup>‡</sup> Abel, J. J., and Crawford, A. C.: On the blood pressure raising constituent of the suprarenal capsule. *Trans. Assn. Amer. Phys.*, 1897, XII, 461-480.

<sup>\*</sup> Cabot, R. C.: Measurements of blood pressure in fevers before, during and after the administration of strychnin. *Trans. Assn. Amer. Phys.*, 1904, XIX, 22-23.

<sup>†</sup> Stengel, A.: Clinical studies in arteriosclerosis. *Trans. Assn. Amer. Phys.*, 1904, XIX, 512-518.

<sup>‡</sup> Stengel, A., and Stanton, W. B.: The heart and circulation in pregnancy and the puerperium. *Ibid.*, 520-553.

not wholly without regret that I find that my personal bibliographic references in this field for the past ten years amount to more than one thousand titles. From this mass of accumulated knowledge of the behavior of the blood pressure in health and disease, what real gain has there been to clinical medicine?

#### I. A METHOD OF OBSERVATION.

A method of sufficient accuracy and sufficient ease of application to satisfy the requirements of medical practice is now available. The contributions toward the elaboration of our present instruments and the methods of their application for the determination of the systolic and the diastolic pressures, and the critical studies to which they have been subjected, are among the most important that I have to record.

To von Basch we owe the first real sphygmomanometer and the first observations of human blood pressure which have any value. Potain<sup>\*</sup> in 1899 made the first important modification by introducing air in place of water as the medium for the transmission of the pressure. In 1896 Riva-Rocci,<sup>†</sup> and in 1897 Leonard Hill,<sup>‡</sup> independently devised the method of circular compression by which the main inaccuracies in the application of the sphygmomanometer were overcome. In 1901 von Recklinghausen<sup>§</sup> demonstrated that the chief error which remained was dependent upon too narrow a compressing arm-let, and introduced the wide cuff which has since become universal. In 1905 Korotkow<sup>||</sup> published his method of auscultatory determination, which has supplanted all other methods for the clinical measurement of the diastolic arterial pressure.

At the present day accurate sphygmomanometers of varying types, to suit the requirements of hospital, consulting room and family practice, are obtainable in every country. An accurate sphygmomanometer consists of a tested manometer, a compressing bag 12 cm. in width for the arm, an inflator fitted with a needle-valve for the slow release of pressure, and connecting tubing. Many types of instrument now discarded have contributed to the production of the present form and have been of great service in the critical study of methods—especially the early instruments of Marey and Mosso, by which diastolic pressures were first approximately studied, the graphic instrument of Erlanger, the various portable instruments of George Oliver, and the instruments of Hill and Barnard and of Gibson. In this country H. W. Cook first introduced a portable form of the Riva-Rocci apparatus. The tonometer of Gärtner was undoubtedly a factor in promoting clinical studies of blood pressure, though its usefulness has passed. As a matter of fact, the auscultatory index for the diastolic pressure has

<sup>\*</sup> Potain: *Arch. de phys. norm. et path.*, 1889, I, 556.

<sup>†</sup> Riva-Rocci, S.: Un nuovo sfigmomanometro. *Gazz. med. di Torino*, 1896, XLVII, 981, 1001.

<sup>‡</sup> Hill, Leonard, and Barnard, Harold: A simple and compact form of sphygmometer or arterial-pressure gauge devised for clinical use. *Brit. Med. Jour.*, 1897, II, 904.

<sup>§</sup> v. Recklinghausen, H.: Ueber Blutdruckmessung beim Menschen. *Arch. f. exper. Pathol. u. Pharmakol.*, 1901, LXVI, 78.

<sup>||</sup> Korotkow: *Berichte der kaiserlichen Militärärztlichen Akademie*. Petersburg, 1905, XII, 395.



made every instrument employing circular compression of the upper arm available for any clinical use.<sup>14</sup>

From among the many studies, critical and experimental, which have contributed to the perfection of the method, to single out those of conspicuous importance in the development of clinical sphygmomanometry is difficult, and to mention them all quite impossible. In this country the work of Erlanger, of Cook and Briggs, and of Stanton is especially important; in England that of Leonard Hill and his various collaborators, of George Oliver, and more recently of MacWilliam and his co-workers. Gallavardin in France, and in Germany, Hensen and Gumprecht were among the pioneers, and von Recklinghausen and Ottfried Müller have rendered conspicuous service. The monographs dealing with the methods and results of blood pressure study have also been valuable in promoting a widespread use of the instrument.<sup>15</sup>

The only significant factor of error which is still inherent in the bloodless measurement of human arterial pressure is due to the resistance of the arterial wall itself. This was first emphasized by Russell,<sup>16</sup> and was so overemphasized as to call forth experimental investigations, which have now determined its importance.<sup>17</sup>

It is altogether probable that in all normal persons and in the vast majority of patients the resistance offered by the

arterial wall to external compression is negligible, but in a few patients with arterial disease such resistance is clearly the cause for overestimation by clinical instruments of the actual blood pressure. As both Gallavardin and MacWilliam have shown, repeated compression of the artery in most of the cases abolishes the local tonus responsible for this error. It is also possible, as MacWilliam has demonstrated and as I have found in my own work, to detect the cases in which this error is important by making both palpatory and auscultatory determinations of the systolic pressure, these patients showing a striking divergence between the two indices. With these exceptions, and the necessary avoidance of excitement and other environmental influences on blood pressure, it is now possible for the clinician to determine with a high degree of accuracy both the maximum or systolic, and the minimum or diastolic, pressure. Thirty years ago only the most approximate measurements of the systolic pressure were possible.

## II. CONTRIBUTIONS TO DIAGNOSIS.

Clinical blood pressure studies have been of greatest value as an aid in diagnosis. Even the earliest and crudest confirmed and greatly extended the older clinical observations on the significance of the high tension pulse in the diagnosis of chronic renal disease. All subsequent studies have emphasized hypertension as a cardinal symptom of chronic Bright's disease—a symptom now more easily detected than any other manifestation of the disease. One has but to turn to Flint's "Practice" to see how completely the sphygmomanometer has revolutionized the diagnosis of this affection. On page 889 the following statement begins the discussion of the diagnosis of chronic Bright's disease: "The diagnosis of chronic as of acute Bright's disease is to be based on the evidence afforded by examination of the urine." Certainly no medical teacher at the present time would regard the urinary findings as the first evidence of this type of renal disease, though recognizing their great importance. The curves from my own blood pressure observations, shown in Charts 1 and 2, strikingly illustrate the diagnostic importance of hypertension in chronic renal disease.

In 1886 the detection of albumin and casts was relatively easy and objective, and the discovery of high blood pressure in many cases difficult and to a large extent dependent upon the special skill of the examiner. At the present day the detection of high blood pressure is absolutely simple and wholly objective, and we have learned how misleading it is to infer from the presence or absence of albumin and casts either the presence or absence of chronic Bright's disease.<sup>18</sup>

With increasing use of the sphygmomanometer all observers

arterial wall on the blood pressure and pulse curves. *Proc. Roy. Soc. Lond.*, 1913, LXXXVI, s. B., 365.

Wells, S. R. and Hill, L.: The influence of the resilience of the arterial wall on the blood pressure and on the pulse curve. *Ibid.*, 180.

<sup>18</sup> Statistical data on this point will be found in my paper, "A Clinical Study of Hypertensive Cardiovascular Disease." *Arch. Int. Med.*, 1913, XII, 755. Also *Trans. Assn. Amer. Phys.*, 1913, XXVIII, 333.

<sup>14</sup> For full discussion and description of methods see Norris: *Blood Pressure, its Clinical Applications*, Phila., 1914, p. 63 *et seq.* Also MacWilliam & Melvin: *Estimation of Diastolic Blood Pressure*, "Heart," 1914, V, 153-196.

<sup>15</sup> The following monographs are worthy of record:

v. Basch, S.: *Die Herzkrankheiten bei Arteriosclerose*. Berlin, 1901.

Potain, C.: *La pression artérielle de l'homme à l'état normal et pathologique*. Paris, 1902.

Oliver, G.: *Studies in blood pressure, physiological and clinical*. Lond., 1902.

Janeway, T. C.: *The clinical study of blood pressure*. New York, 1904.

Pal, J.: *Gefässkrisen*. Leipz., 1905.

Müller, O.: *Der arterielle Blutdruck und seine Messung beim Menschen*. *Ergeb. d. inn. Med. u. Kinderheilk.*, 1908, II, 367-417.

Gallavardin, L.: *La tension artérielle en clinique*. Paris, 1910.

Horner, A.: *Der Blutdruck des Menschen*. Leipz., 1913.

Norris, G. W.: *Blood pressure: its clinical applications*. Phila., 1914.

A full literature will be found in these monographs.

<sup>16</sup> Russell, W.: *Arterial hypertonus, sclerosis and blood pressure*. *Edinb. and Lond.*, 1908, p. 87.

<sup>17</sup> Since the study presented by Park and myself before this association in 1910 (*An experimental study of the resistance to compression of the arterial wall*. *Arch. Int. Med.*, 1910, VI, 586), the following important publications have appeared:

Gallavardin, L. and Haour, J.: *Baisse systolique de la tension artérielle au moment de la mensuration*. *Arch. d. mal. du cœur*, 1912, V, 81.

MacWilliam, J. A. and Kesson, J. E.: *The estimation of systolic blood pressure in man with special reference to the influence of the arterial wall*. "Heart," 1913, IV, 279.

MacWilliam, J. A., Kesson, J. E. and Melvin, S.: *The conduction of the pulse wave and its relation to the estimation of systolic blood pressure*. *Ibid.*, 393.

Hill, L. and Flack, M.: *The effect of lability (resilience) of the*



began to encounter patients with hypertension without the urinary evidences of nephritis and without renal symptoms. Such patients had previously been supposed to suffer from idiopathic hypertrophy of the heart. The opinion has gradually developed that a symptom-complex exists in which the symptom first in importance and in time of development is increased arterial pressure. Patients presenting this symptom-complex suffer, as a rule, from minor grades of myocardial insufficiency or from cerebral symptoms, or present an indefinite neurasthenic state. Evidences of renal insufficiency are conspicuously absent during the earlier stages. The condition has been given various names—latent *angiosclerosis* by von Basch, *presclerosis* by Huchard, *hyperpiesis* by Allbutt. I have preferred to call it *primary hypertensive cardiovascular*

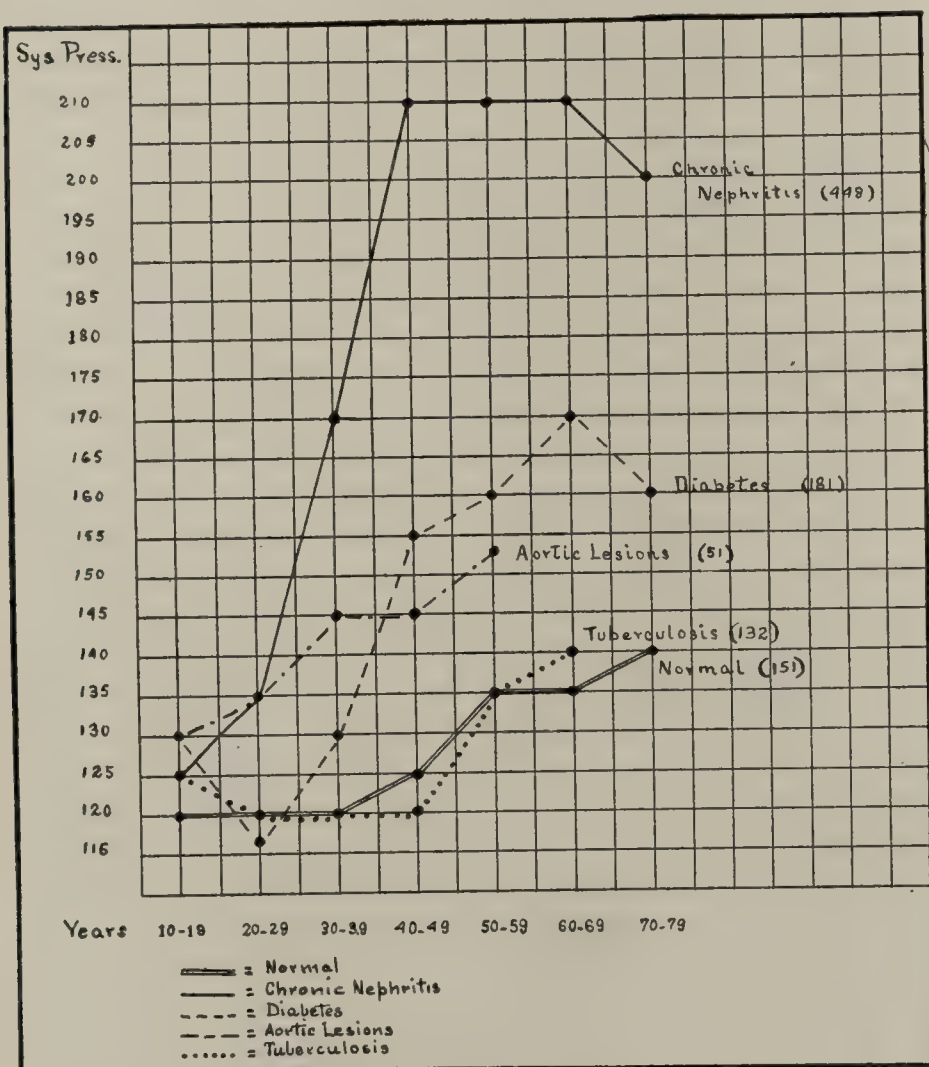


CHART 1.—Median systolic blood pressures, arranged by age periods. Personal observations. (Figures in brackets at right of curves indicate total number of individuals observed in each group.)

disease. It is often spoken of merely as *hypertension* or *essential hypertension*, and has recently been designated *benign essential hypertension* by Volhard and Fahr.<sup>19</sup> It has therefore neither a uniformly accepted name nor a universally accepted interpretation, but is everywhere recognized as one of the commonest types of circulatory disease. This recognition is due entirely to the sphygmomanometer.

Those who dislike terms which express a functional and not an anatomical diagnosis have included these cases either in

<sup>19</sup> Volhard, F. and Fahr, Th.: Die Brightsche Nierenkrankheit. Berlin, 1914.

the category of chronic nephritis or of arteriosclerosis. The careful study of the blood pressure in each of these conditions, however, does not warrant the view that the continued existence of the symptom hypertension is in itself sufficient ground for the diagnosis of one or the other of them in the sense in which the terms are ordinarily used. I have already discussed this at length elsewhere.<sup>20</sup> Suffice it to say here that all observers agree that widespread sclerosis of the accessible peripheral arteries or of the aorta may exist with normal or low blood pressure. Therefore hypertension is not a necessary sequence of ordinary arteriosclerosis. On the other hand, while the study by finer methods of the kidneys of such patients as die has shown that in almost all of them some changes in the smaller renal vessels and in the glomeruli can be made out,<sup>21</sup> nevertheless there is no parallelism whatever between the extent of the kidney lesions and the height of the blood pres-

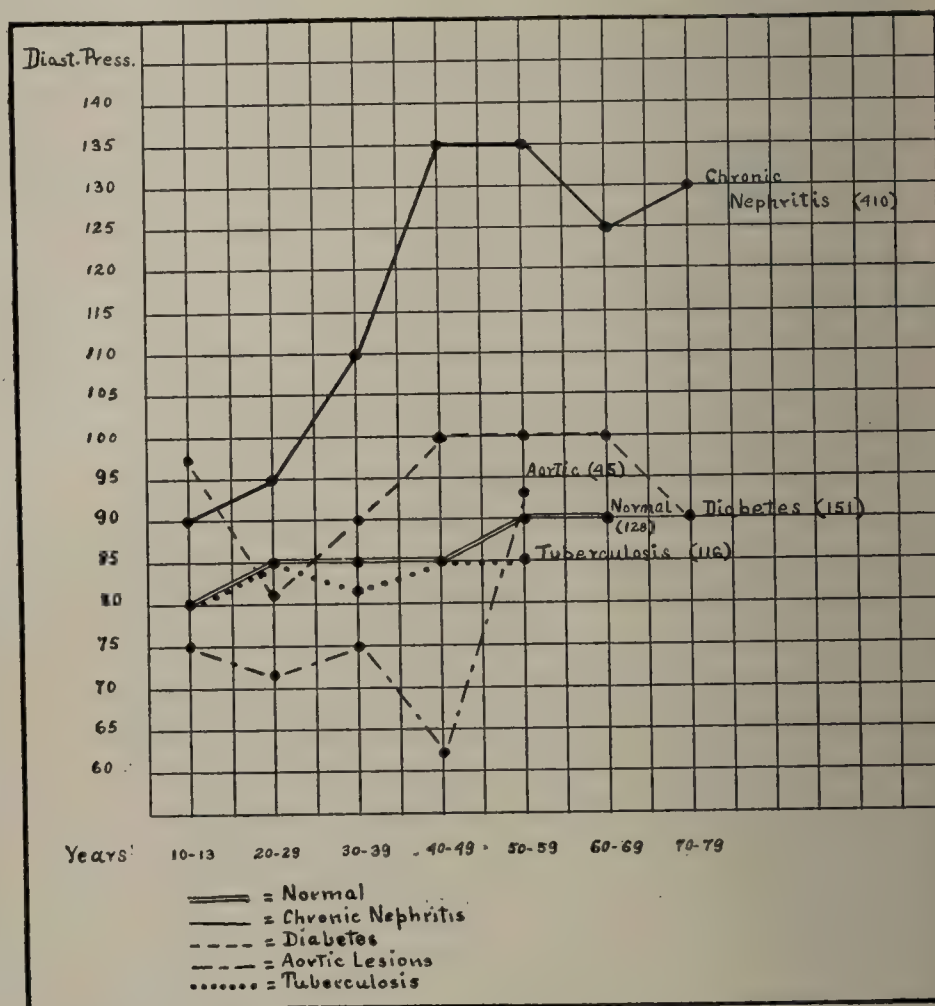


CHART 2.—Median diastolic blood pressures, arranged by age periods. Personal observations. (Figures in brackets at right of curves indicate total number of individuals observed in each group.)

sure. In the end-stages these patients may certainly exhibit the anatomical picture of the primary contracted kidney. In the early stages, however, as Jores has so clearly pointed out,<sup>22</sup> the kidney is only one of the organs implicated in the wide-

<sup>20</sup> Janeway, T. C.: Nephritic hypertension; clinical and experimental studies. Amer. Jour. Med. Sci., 1913, CXLV, 625.

<sup>21</sup> Fischer, J.: Ueber die Beziehungen zwischen anhaltender Blutdrucksteigerung und Nierenerkrankung. Deutsch. Arch. f. klin. Med., 1913, CIX, 469.

<sup>22</sup> Jores, L.: Ueber die Arteriosklerose der kleinen Organarterien und ihre Beziehungen zur Nephritis. Virchows Arch., 1904, CLXXVIII, 367.



spread disease of the arterioles, and may show but little change. To consider essential hypertension, therefore, wholly of renal origin is unwarrantable at the present time; and a functional designation may be wisely retained, unless the term "arteriolar sclerosis" can find acceptance.

The foregoing condition occurs frequently after middle life, but is peculiarly common in elderly diabetics (see Charts 1 and 2). On the other hand, it is clear from my own observations and those of Elliott<sup>23</sup> that diabetes itself is without influence on the arterial pressure. Hypertension is therefore presumably an expression of the well-known tendency of diabetics of suitable age to develop arterial disease; or possibly in some cases arterial disease is the cause of the lesions responsible for the diabetes.

In the differential diagnosis of the type of existent renal disease blood pressure observation plays a conspicuous part. Great stress has been laid upon this by Volhard and Fahr in their recent monograph.<sup>24</sup> Without going quite to the same length of schematic differentiation, it can be said that, in patients presenting the other evidences of kidney disease, increased blood pressure always suggests either primary disease of the vessels or true diffuse nephritis. As I have seen hypertension develop during the early anuria of necrosis of the kidney from bichloride of mercury, however, I do not believe, as they do, that it can be considered as absolutely differentiating between the degenerative nephroses on the one hand and the inflammatory nephritides and vascular scleroses on the other. A persistently subnormal blood pressure in a patient with renal symptoms is certainly the strongest evidence of amyloid kidney. In clinical acute Bright's disease hypertension regularly indicates a true diffuse nephritis or a severe renal insufficiency.

Of less diagnostic value, but still a real contribution to clinical medicine, has been the study of blood pressure in increased intracranial tension. This has been thoroughly elucidated by animal experimentation. In the differential diagnosis of coma, hypertension always suggests cerebral hæmorrhage acting in this way, or uremia associated with a pre-existing hypertensive nephritis.

Transient hypertension has been exhaustively studied by Pal.<sup>25</sup> Of the so-called vascular crises which we have learned to recognize, that accompanying puerperal eclampsia is the most important. Blood pressure studies have strikingly confirmed the early observations of Vaquez<sup>26</sup> that a persistent hypertension after the delivery of the child points to eclampsia as probable. Similarly, hypertension has been shown to accompany lead colic and the gastric crises of tabes, and has some diagnostic value in cases of obscure abdominal pain. Exoph-

thalmic goitre is associated with moderate elevation of blood pressure in a large proportion of cases.

In the diagnosis of the other forms of circulatory disease, blood pressure studies have yielded little of importance. Normal blood pressure in a patient with myocardial insufficiency without valvular disease helps materially toward the diagnosis of primary disease of the myocardium. It is a striking fact, however, as Starling<sup>27</sup> and others have shown, that a moderate hypertension commonly accompanies myocardial insufficiency, the pressure falling as the circulation improves.

In the study of the valvular diseases of the heart, blood pressure observation has proved valuable only in the diagnosis of aortic regurgitation. This is facilitated in two ways; first, by the demonstration of the increased pulse pressure in those cases which do not show a typical collapsing pulse (see Charts 1 and 2), and second, by the very interesting finding, first made by Hill and Flack,<sup>28</sup> that the systolic blood pressure in the leg in aortic regurgitation is regularly higher than in the arm—sometimes to an astonishing extent. I am personally convinced of the diagnostic value of this discrepancy between arm and leg pressures, which does not seem to be found in other pathological conditions or in normal individuals when due precautions are taken.

As an aid to clinical diagnosis subnormal blood pressure has been of relatively little value. While it commonly accompanies the infectious diseases and cachectic states, it is but one of many symptoms and the diagnosis does not depend upon its discovery. In the recognition of amyloid disease and of Addison's disease, however, a persistently low blood pressure is of very real importance. In the detection of internal hæmorrhage the discovery of a falling arterial pressure, and especially of a falling pulse pressure and pulse rate, as described by Wiggers,<sup>29</sup> may be significant. A fall in pressure during pleural aspiration has been shown by Capps and Lewis<sup>30</sup> to be an indication of reflex inhibition of the heart or vasomotor center. The relation of low blood pressure to surgical shock, while of great value to the surgeon, is beyond the limits of this paper.

The early investigators of blood pressure, especially in

<sup>27</sup> Starling, H. J.: Observations on the arterial blood pressure in heart disease. *Lancet*, 1906, II, 846.

<sup>28</sup> Hill, L. and Flack, M.: The accuracy of the obliteration method of measuring arterial pressure in man. *Proc. Physiol. Soc., Lond.*, 1908-9, p. 48.

These observations have been confirmed by Hare (*The Difference between Systolic Pressure in the Arm and in the Leg in Aortic Regurgitation. Trans. Assn. Amer. Phys.*, 1910, XXV, 91), by Hill and Rowlands (*Systolic Blood Pressure in Cases of Aortic Regurgitation. "Heart,"* 1912, III, 219), by Rolleston (*On the Systolic Blood Pressure in the Arm and Leg in Aortic Incompetence. Ibid.*, 1912, IV, 83) and by Murray (*Systolic and Diastolic Blood Pressure in Aortic Regurgitation. Brit. Med. Jour.*, 1914, 697).

<sup>29</sup> Wiggers, C. J.: The prognostic significance of pulse-pressure changes during hæmorrhage. *Arch. Int. Med.*, 1910, VI, 281.

<sup>30</sup> Capps, J. A. and Lewis, D. D.: Blood pressure lowering reflexes from irrigation of the chest in emphysema. *Trans. Assn. Amer. Phys.*, 1909, XXIII, 188.

<sup>23</sup> Elliott, A. R.: A clinical study of blood pressure variations in diabetes and their bearing on the cardiac complications. *Jour. Amer. Med. Assn.*, 1907, XLIX, 27.

<sup>24</sup> Volhard, F. and Fahr, Th.: *Die Brightsche Nierenkrankheit*. Berlin, 1914.

<sup>25</sup> Pal, J.: *Gefässkrisen*. Leipzig, 1905.

<sup>26</sup> Vaquez and Nobécourt: De la pression artérielle dans l'éclampsie puerpérale. *Bull. et mém. Soc. méd. d. hôp. de Paris*, 1897, XIV, 117.



France, beginning with Marfan,<sup>31</sup> believed low blood pressure to be an important indication of tuberculosis. Norris<sup>32</sup> still states that tuberculosis is generally associated with hypotension. My own observations have convinced me that as a factor in the diagnosis of tuberculosis blood pressure measurements have no real value. A glance at the curves in the accompanying charts (Charts 1 and 2) shows in striking fashion the essential correspondence of the curve of the normal and the curve of the tuberculous individuals, as observed in an office practice. Shalet,<sup>33</sup> who has examined about 1000 patients at the Otisville Sanatorium, has come to the same conclusion. It is of course unquestionable that in advanced and febrile tuberculosis a low blood pressure exists and has the same significance as in other active infections.

Is there a state of constitutional or essential hypotension, as there is of essential hypertension, as has been held by Bishop and a few other observers?<sup>34</sup> At the present time I am not convinced of this, for I have personally observed systolic pressures which would ordinarily be considered subnormal—below 110 in men and 95 to 100 in women—existing over long periods of absolutely perfect health and physical activity. Low blood pressure, in the cases to which the term “constitutional low blood pressure” has been applied, is merely one symptom of lowered tone of the central nervous system—though possibly an important one to recognize.

For the final determination of the importance of slight deviations from the average blood pressure in normal individuals a knowledge of the limits of normal variation is essential. Its attainment necessitates a vast number of observations and has therefore taken much longer than the acquisition of a knowledge of the more marked pathological changes in pressure. The real basis has been afforded by the introduction of the sphygmomanometer in life insurance examinations. Since the publication by Fisher<sup>35</sup> of the blood pressure records of 19,339 accepted candidates for life insurance, all previous

tabulations of average pressures in normal adults can be discarded as inadequate. Fisher's table follows:

Ages	Number	Average Blood Pressure
15-20	281	119.85
21-25	785	122.76
26-30	791	123.65
31-35	689	123.74
36-40	2,111	126.96
41-45	6,740	128.56
46-50	4,471	130.57
51-55	2,371	132.13
56-60	1,100	134.78
Totals	19,339	128.91

Dr. Fisher has written me personally that since this publication he has been informed of a record of 9000 readings by another company which did not vary one millimeter in the average of any age from those he has tabulated—making an average standard based upon the observation of over 28,000 healthy adults. However, for the decision that a particular blood pressure reading is beyond the possible normal it is necessary to know not only the normal average but the limits of variation at any age. This must be so much a matter of opinion as to the health of the individual showing a debatable abnormal blood pressure that there will always be a difference of opinion about it. I am inclined to revise my former opinion and to agree with Cook,<sup>36</sup> and Lauder Brunton before him, that over 135 mm. up to middle life, and 145 or 150 mm. thereafter, should be regarded as pathological hypertension if found on repeated examinations. For the lower limits of normal pressure in adults I should take 100 mm. in women and 105 to 110 in men, though attaching less significance to occasional readings slightly below this.

The diastolic pressure is unquestionably of great importance, and in the determination of abnormally high or low blood pressure should have equal consideration, but it is as yet so little used that a consideration of it would go beyond the scope of the present paper (see Chart 2).

The tabulation of my personal blood pressure readings in persons without detectable disease, as shown in Charts 1 and 2, is interesting as showing how closely a comparatively small series of observations may follow the averages obtained in such a large series as Fisher's. Of course, the smaller the series the less smooth the curve, but the figures are strikingly similar.

All figures for the normal individual bring out clearly the definite tendency of the blood pressure to increase with advancing years. The effect of age, however, is most strikingly seen in childhood, and within recent years a large number of important studies on blood pressure in children has been published.<sup>37</sup> In this particular field of study the oscillatory method—which I believe gives erroneous results in adults—has found a special application, because neither the palpatory nor the auditory

<sup>31</sup> Marfan, B. J. A.: De l'abaissement de la tension artérielle dans la phthisie pulmonaire. *Compt. rend. Soc. de biol., Par.*, 1891, III, 346.

La tension artérielle dans la tuberculose pulmonaire chronique et son importance pour le pronostic. *Rev. d. méd.*, 1907, XXVII, 1005.

<sup>32</sup> Norris, G. W.: Blood pressure; its clinical applications. *Phila.*, 1914, p. 199.

<sup>33</sup> Shalet, L.: Blood pressure in pulmonary tuberculosis. *New York State Jour. Med.*, 1914, XIV, 189.

<sup>34</sup> Bishop, L. F.: Constitutional low arterial tension in children. *Ann. Gynec. and Pediat.*, 1906, XIX, 85. Also *Jour. Amer. Med. Assn.*, 1906, XLVII, 1734. Constitutional low arterial tension and its relation to the life of the individual. *New York Med. Jour.*, 1906, LXXXIII, 967.

Goodman, E. H.: Some cases of hypotension associated with a definite symptomatology. *Amer. Jour. Med. Sci.*, 1914, CXLVII, 503.

Norris, G. W.: Blood pressure: its clinical applications, Chap. VI. Essential hypotension (constitutional low arterial pressure).

<sup>35</sup> Fisher, J. W.: The diagnostic value of the sphygmomanometer in examinations for life insurance. *Jour. Amer. Med. Assn.*, 1914, LXIII, 1752.

<sup>36</sup> Cook, H. W.: Blood pressure in prognosis. *Med. Rec.*, 1911, LXXX, 959.

<sup>37</sup> Durand-Viel, P.: Des variations de la pression artérielle au cours de quelques maladies chez les enfants. *Paris*, 1903.

Stone, J. S.: Report on blood-pressure determinations made at



index of blood pressure can be readily used in very small children. The accompanying chart (Chart 3) from Koessler's article shows very clearly the rapid rise of pressure during the growth period of the child. In using it for absolute values, however, one must remember that the oscillometric method gives an overestimation of the systolic pressure. The majority of those who have studied this aspect of the question agree with Wolfensohn-Kriss, that the chief parallelism of the blood pressure in childhood is with the increasing height and body weight rather than with age itself, and that the slightly lower pressure seen in girls and in women, when compared with males of the same ages, is related to the lesser height and weight rather than to sex itself.

An interesting study has been made by Wildt<sup>33</sup> of blood pressure in the aged. He found the following average blood pressures:

Ages	Systolic	Diastolic
60-64	137	76
65-69	143	78
70-74	148	80
75-79	152	82
80-84	148	78
85-89	162	85
90-96	129	59

These averages represent readings on 250 individuals, without the exclusion of those who showed circulatory or other dis-

the Boston Children's Hospital. Div. Surg., Harvard Med. School, 1903-4, I, Bull. No. II, 18.

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Seiler, F.: Praktische Bemerkungen über den Blutdruck und über Normalwerte des Blutdruckes im Kindesalter. *Cor.-Bl. f. Schweiz. Aerzte*, 1910, XL, 433.

Wolfensohn-Kriss, P.: Ueber den Blutdruck im Kindesalter. *Arch. f. Kinderh.*, 1910, LIII, 332.

Salle, V.: Ueber Blutdruck im Kindesalter. *Jahrb. f. Kinderh.*, 1911, LXXIII, 273.

Jarricot: Mesure de la tension artérielle chez les enfants et oscillomètre de Pachon comme sphygmo-signal. *Péd. prat.*, 1912, X, 392.

Koessler, L.: L'oscillimétrie appliquée à l'étude de la tension artérielle chez les enfants. Paris, 1912, No. 144.

Balard, P.: Le pouls et la tension artérielle de l'enfant et du nouveau-né. *Gaz. des hôp.*, Paris, 1913, LXXXVI, 837.

Friberger, R.: Ueber die Entwicklung von Puls und Blutdruck im späteren Kindesalter. *Arch. f. Kinderh.*, 1913, LX, 331.

Katzenberger, A.: Puls und Blutdruck bei gesunden Kinder. *Kinderh.*, 1910, IX, 257.

Leitao, M.: Pression artérielle chez l'enfant. *Arch. d. méd. d. enf.*, 1913, XVI, 102.

Judson, C. F. and Nicholson, P.: Blood pressure in normal children. *Amer. Jour. Dis. Children*, 1914, XII, 257.

<sup>33</sup> Wildt, H.: Ueber Blutdruck im Greisenalter. *Zentralbl. f. Herzkrankh. u. Gefässkrankh.*, 1912, IV, 41.

ease. The percentages showing marked hypertension in this group were as follows:

Ages	Systolic Pressures	
	Over 150	Over 200
65-69	49%	3%
70-74	44%	6%
75-79	39%	7%
80-84	38%	12%
85-89	64%	14%

These pressures were quite regularly associated with chronic nephritis or arteriosclerosis. Hypotension he found only in tuberculosis and pneumonia, in six cases of contracted kidney and in individuals with weak hearts. There was a regular tendency for the amplitude or pulse pressure to increase, the diastolic pressure frequently being lower than in earlier life.

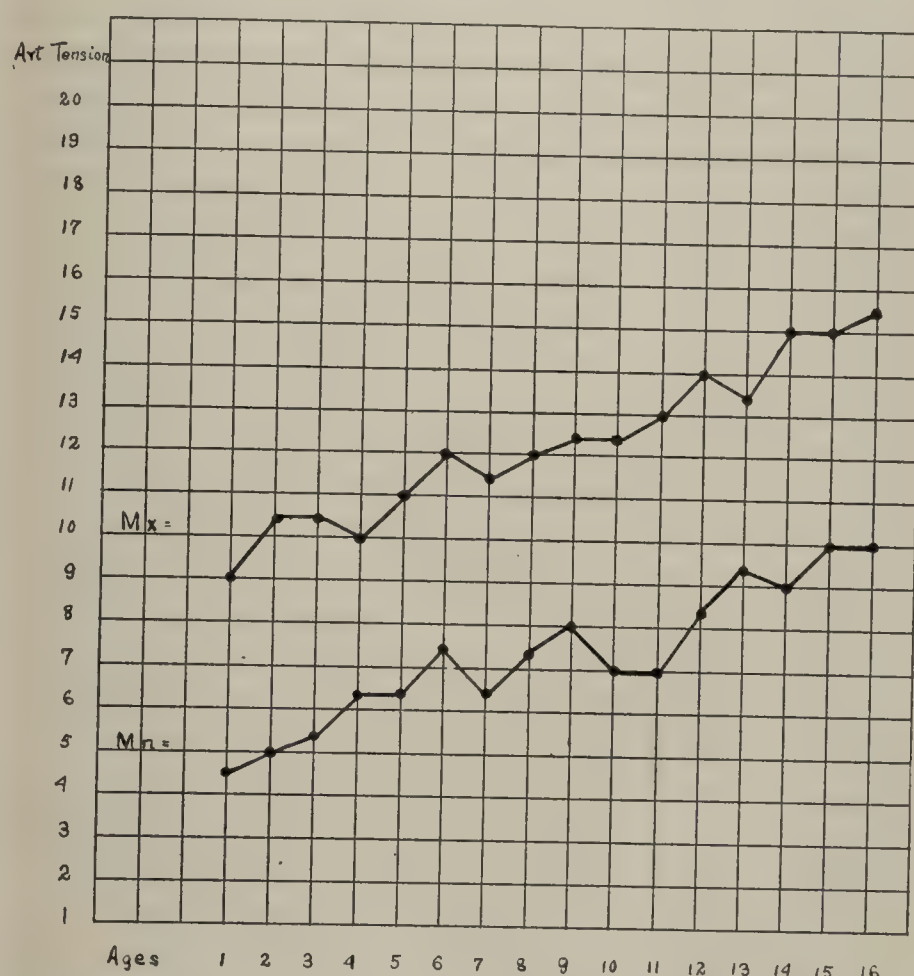


CHART 3.—Curve of pressures arranged by ages (boys), from "L'Oscillométrie appliquée à l'étude de la tension artérielle chez les enfants," L. Koessler, Paris, 1912, p. 65.

It is interesting that in the four individuals above ninety the pressure was much lower than at the preceding age periods.

An important observation on blood pressure in the normal adult male has been made by Chamberlain<sup>34</sup> in the Philippines, showing, from the examination of 992 American soldiers, that the average pressures in the tropics are lower than the normal averages for temperate climates and that the pressure was lower during the first three months of tropical residence than

<sup>34</sup> Chamberlain, W. P.: A study of the systolic blood pressure and the pulse rate of healthy adult males in the Philippines. *Phil. Jour. Sci.*, 1911, VI, 467.



subsequently, and on the average about 3 to 5 mm. lower during the hottest season of the year. His table is as follows:

Ages	Number	Average Blood Pressure
18-20	36	115
20-25	469	114.3
25-30	286	115.9
30-35	109	116.7
35-40	58	120.5
Over 40	34	119.6

He failed to find any marked parallelism between blood pressure and the height and weight of the individual. The mean pressure of Philipinos during the same age periods did not differ from that of Americans.

### III. CONTRIBUTIONS TO PROGNOSIS.

So far, the most important application of blood pressure measurements to the solution of prognostic problems has been made by the life insurance companies. This is quite natural, since the entire business of life insurance is based upon scientific prognosis. Only recently, however, have actuaries attempted to make statistical studies of prognosis in disease, and the results of this application of statistics, on a scale sufficiently large to reduce the influence of individual error and variation to a negligible quantity, are of great importance to the medical profession. Physicians rarely have the opportunity to observe hypertensive patients until they develop symptoms, whereas the life insurance examiner has the opportunity to detect these conditions before any other evidence of deviation from the normal exists. During the years from 1907 to 1910, the company of which Dr. Fisher is medical director accepted 2,661 applicants, with an average blood pressure of 142.43, between the ages of 40 and 60, and their average mortality was practically the mortality of all of the insured. During the same period the company accepted 525 persons with an average pressure of 152.58, or only 10 mm. above the average of accepted risks. These persons showed a mortality 30% above the general average of the company. They rejected 1,970 applicants with an average pressure of 161.44 between the years 1907 and 1913, and, when followed up, these have shown a mortality more than double the average for the company—and this is probably below the facts, because of incomplete returns.<sup>35</sup>

These figures are eloquent testimony to the value of the instrumental measurement of blood pressure in the early recognition of what is frequently the sole evidence of a deviation from the normal in middle-aged persons. Fisher states that but little value is attached as yet to their observations of low pressure.

Apart from the general indication which hypertension gives of the eventual probability of the development of symptoms of myocardial insufficiency, renal insufficiency or cerebral vascular disease, the study of blood pressure has not yet led to important gains in the ability to predict duration of life. In particular, it is clearly a mistake, as I have emphasized in a

previous report before this association,<sup>40</sup> to assume that an individual with extreme hypertension will die sooner than one with a moderate elevation of blood pressure. The blood pressure reading is an additional factor to be combined by the physician with all the other symptoms and signs presented by the patient in arriving at that most difficult of practical judgments, a prognosis as to the duration of life. Rapidly falling blood pressure is a frequent terminal symptom in hypertensive patients dying of uræmia, and, as in apoplexy, is a very bad omen. I have also found a steady rise in pressure to be a serious feature in cases of chronic diffuse nephritis, usually indicating the development of severe renal insufficiency.

In the early days of blood pressure study I, like most physicians interested in this field, hoped that it would furnish most important indications in acute infectious disease. That hope has been disappointed. I think that most of us must now agree with the conclusions of Kurt Weigert<sup>41</sup> from his extensive studies of the various acute infections, and which have been confirmed, for scarlet fever, by Rolleston,<sup>42</sup> that the value of the blood pressure measurement for prognosis in the acute infectious diseases is slight. It is an additional factor which is occasionally useful, as in typhoid patients with hemorrhage; but for the most part the simpler observations made by our predecessors in clinical medicine, of the facies, the tongue, the pulse, the heart sounds and the state of the nervous system make the prognosis equally well without a knowledge of the blood pressure curve. That further observations may permit of greater refinement in this field is not to be denied.

In one disease—lobar pneumonia—so good an observer as Gibson<sup>43</sup> thought he had discovered a most important prognostic indication in the relation of blood pressure and pulse rate, which has become known as Gibson's rule. The rule is that, when the blood pressure, expressed in millimeters of mercury, falls below the pulse rate per minute, expressed in figures, the prognosis is unfavorable. But a recent critical study by Newburgh and Minot<sup>44</sup> has shown that the prognostic inferences based on Gibson's rule were oftener wrong than right in their 15 cases. They emphasize the fact that low systolic pressures are not "invariably of evil omen," and in this I heartily concur.

### IV. CONTRIBUTIONS TO THERAPEUTICS.

In the progress of practical medicine, advances in the diagnosis of disease have usually preceded advances in therapeutics, often by a very long period. In the treatment of diseases

<sup>40</sup> Janeway, T. C.: A clinical study of hypertensive cardiovascular disease. *Arch. Int. Med.*, 1913, XII, 755. Also *Trans. Assn. Amer. Phys.*, 1913, XXVIII, 333.

<sup>41</sup> Weigert, K.: Ueber das Verhalten des arteriellen Blutdrucks bei den akuten Infektionskrankheiten. *Samm. klin. Vortr.*, 1907, No. 459 (*Inn. Med.*, No. 138, 65).

<sup>42</sup> Rolleston, J. D.: Blood pressure in scarlet fever. *Brit. Jour. Child. Dis.*, 1912, IX, 444.

<sup>43</sup> Gibson, G. A.: Some lessons from the study of arterial pressure. *Edinburgh Med. Jour.*, 1908, n. s., XXIII, 17.

<sup>44</sup> Newburgh, L. H., and Minot, G. R.: The blood pressure in pneumonia. *Arch. Int. Med.*, 1914, XVI, 48.



associated with high blood pressure the ability to detect hypertension led at first to widespread abuse of vaso-dilators. Further study, however, clearly showed both the difficulty of permanently lowering the blood pressure by drugs and the occasional harm produced in these patients by successful vaso-dilatation; and, as a result, the treatment of essential hypertension today is the treatment of the patient and not of the hypertension—safe-guarding treatment in the strictest sense—the endeavor is to avoid myocardial or renal insufficiency, or a vascular accident, and to limit the operation of known causes for hypertension.

The most remarkable claims for the therapeutic control of hypertension have been made by physicians employing the so-called "d'Arsonvalization," a special form of high frequency current. A critical study of this whole literature has been to me far from convincing. A vast majority of the publications have been by Moutier. He has used very inaccurate instruments for the measurement of blood pressure. In his most important account of 50 cases treated,<sup>45</sup> in 43 the fall in pressure could have been explained by the well-known tendency for first readings to be higher than subsequent ones, and could be duplicated from my records of untreated cases. Of his remaining seven cases, in only five was there any reduction in pressure which could be considered at all permanent, and in not a single case was there any fore-period of observation to determine the spontaneous variations, which, in hypertensive patients, may assume considerable proportions.

A study of 266 cases of arteriosclerosis by Bühler<sup>46</sup> is on its face rather more convincing. The few patients in whom I have been able personally to control the effects of this treatment, unknown to the physician who was administering it, have shown no result whatever, although a marked effect was claimed by the electro-therapist. The whole subject, however, is deserving of scientific and objective investigation.<sup>47</sup>

Until the real mechanism by which high blood pressure is produced shall be thoroughly understood, neither preventive nor curative treatment can be developed. The use of the sphygmomanometer has, however, contributed largely to the more careful study of these patients, and thus indirectly to their more intelligent treatment. It affords a means of gauging objectively the necessary dose of a vaso-dilator when one must be used—and incidentally has given proof of the inertness of many of the preparations of vaso-dilating drugs upon the market. Thus blood pressure studies, from the standpoint of therapeutics, have been largely critical and negative.

They have been of great importance in respect to one drug, digitalis. That digitalis—a pharmacological action of which in the intact animal is to produce marked vaso-constriction—

does not tend uniformly to raise the blood pressure in hypertensive patients with myocardial insufficiency, or, if it does, improves the circulation at the same time, has been especially emphasized by Sahli,<sup>48</sup> and has gradually become common knowledge.<sup>49</sup> This is a matter of the first importance, because we have no substitute for the digitalis bodies in myocardial insufficiency.

Control by the sphygmomanometer of the so-called cardiac or circulatory stimulants has shown how misplaced has been the faith of physicians in such drugs as strychnine and caffeine as a means of combating circulatory failure in acute infectious diseases or in surgical shock.<sup>50</sup> The various hydrotherapeutic procedures have been studied in the same way, and a large literature is growing up on the subject.

In the treatment of acute infectious disease I think we must still agree with Weigert<sup>41</sup> that knowledge of the blood pressure does not help us, though this may be because of inadequate development of the methods for measuring the pulse pressure. It is possible that a very careful critical study of systolic, diastolic and pulse pressures may give the observation of the arterial pressure a greater importance in acute diseases than it possesses today.

#### V. CONTRIBUTIONS TOWARD A FUNCTIONAL PATHOLOGY OF THE CIRCULATION.

In my opinion the clinical study of blood pressure during the past 30 years has justified the time devoted to it, as much by its contribution to medical theory as by its contribution to medical practice. Prevention of disease must always depend upon a knowledge of causation and transmission, and its adequate treatment upon a complete understanding of the mode of production of the lesions and the symptoms which together constitute the phenomena of disease. The problem of the etiology of the chronic so-called degenerative diseases is one of the greatest awaiting solution at the present day, and the first approach to it must be from the standpoint of accurate clinical observation. Clinical medicine, not animal experimentation, determines and defines the problem.

The accurate measurement of the blood pressure in patients with cardiovascular disease has afforded a mass of incontrovertible facts, which are essential for the attainment of a sound functional pathology of the circulatory system. Increased blood pressure has been found to be the earliest and the most important functional disturbance in a very common type of circulatory disease. Its association with certain lesions of the

<sup>48</sup> Sahli, H.: Ueber Herzmittel und Vaso-motorenemittel. Kong. f. inn. Med. Verhandl., 1901, XIX, 45.

<sup>49</sup> Martinet, A.: Pressions artérielles et viscosité sanguine. Paris, 1912.

Lawrence, C. H.: The effect of digitalis on the blood pressure and pulse pressure in the presence of cardiac decompensation. Boston Med. & Surg. Jour., 1914, CLXX, 37.

Janeway, T. C.: The comparative value of cardiac remedies. Arch. Int. Med., 1914, XIII, 361.

<sup>50</sup> Newburgh, L. H.: The use of strychnine and caffeine as cardiovascular stimulants in the acute infectious diseases. Arch. Int. Med., 1915, XV, 458.

Crile, G. H.: Blood pressure in surgery. Phila., 1903.

<sup>45</sup> Moutier, A. and Challamel, A.: Sur 50 nouveaux cas d'hypertension artérielle permanente traités par la d'arsonvalization. Ann. d'électrobiol., 1904, VII, 657. Also Rev. d. mal de la nutrition, 1905, III, 82.

<sup>46</sup> Bühler, A.: Erfolge der Hochfrequenzströme bei Arteriosklerose. Med. Klin., 1914, X, 55.

<sup>47</sup> For further literature on therapeutics in hypertension see Norris: "Blood Pressure: Its Clinical Application," Chap. XIII, p. 273.



arteries, in the kidneys and elsewhere, has been determined. Its development has been traced in other cases where obvious renal disease has preexisted. In a considerable number of cases the evidence strongly suggests that the increased arterial pressure develops parallel with changes in the arteries rather than as their sequel. Many associations of temporarily high blood pressure with intoxications and other abnormal conditions have been discovered. In addition, the effects of myocardial insufficiency, of acute infections, and of other complicating disturbances in lowering a persistent hypertension are being worked out in greater and greater detail. Accessory hypertensive influences are being similarly described with greater completeness. The problem of the cause of the hypertrophied heart in chronic Bright's disease engrossed the generation preceding ours. For us it has become the problem of the cause and the pathological physiology of permanent hypertension. This is more than a change in emphasis. It means an accumulation of exact knowledge derived from clinical observation by a physiological method which has already enlarged our understanding of a pathological process, of which the lesion in the heart is an end result, and has brought the problem one step nearer solution.

In spite of the considerable advance in our knowledge of the modes of production of hypertension in animals and the remarkable discoveries concerning the action of the adrenals

and other ductless glands, the problem of the causation of hypertension still awaits solution. The clinical observation of blood pressure by family practitioners over a long period of years, now that the sphygmomanometer has become a routine instrument, may yet contribute data of importance toward this much desired end.

From a purely negative standpoint the discovery that myocardial insufficiency, as in valvular diseases of the heart, results in a great reduction in the arterial blood mass but not in arterial blood pressure, while at first sight disappointing to physicians seeking only aid in the immediate practical problems of medicine, is an important fact in circulatory pathology. It shows the presence of a compensatory vasomotor mechanism in cardiac disease. In states of supposed circulatory collapse in acute infectious disease the same disappointment has been met with. The sphygmomanometer has failed to reveal the expected extreme hypotension until the agonal period. But the sphygmomanometer has given us facts in place of inferences from crude methods. Similarly, graphic and electrical methods are refining the analysis of the cardiac rhythms. From these facts, when combined with like accurate observations by other physiological methods, there will yet be constructed a functional pathology of the circulation which will be the basis for the successful treatment of patients with circulatory disease.

## ELUSIVE MOBILITY OF THE BREAST IN A CASE OF RETRO-MAMMARY CYST.

By W. S. HALSTED, M. D.

Surgical No. 36,939. Large healthy woman, æt. 43. Admitted to The Johns Hopkins Hospital, May 4, 1915.

About four weeks before admission the patient noticed, quite accidentally, on palpation, an abnormal hardness in the upper half of the right breast. She could not recall having had the slightest pain in either mammary gland.

*Examination.*—Both breasts were rather voluminous, the right slightly larger than the left. On inspection there was a faint suggestion of fulness about the middle of the upper hemisphere of the right mamma. On palpation a fairly well defined area of induration, measuring approximately 9 x 7 cm., was found. The lower margin of the mass corresponded quite accurately to the horizontal nipple-line. The tumor was very hard and seemed to be inelastic. There was no retraction of the nipple, no evidence of shortening of the subcutaneous trabeculæ on widest excursions of the breast and, in brief, none of the signs of carcinoma. Glandular tissue of considerable thickness apparently intervened between the skin and the hard mass, the margins of which seemed finely roseate.

There was, however, one remarkable manifestation. Several times in the course of the examination, at the moments when the tumor's elasticity was being tested by the exercise of particularly firm pressure, the breast, suddenly, would make an

elusive glide outwards under my fingers. This was so surprising that I commented on it to my assistants. At the final examination, on the operating table the same thing occurred, and my associate, Dr. Heuer, who assisted at the operation, remarked that he, too, had been surprised while making his examination to note this abnormal slipping of the breast on the chest wall. As a possible explanation of the phenomenon I suggested retro-mammary cyst. This the tumor proved to be.

Glandular tissue, a centimeter or more in thickness, was cut through before the cyst was punctured. The posterior wall of the cyst was very thin, perhaps one quarter of a millimeter thick, and protruded hernia-like from the under surface of the breast. The precise size and shape of the projecting part of the evacuated cyst could not well be determined. We surmised that it had been hemispherical in shape and about the size of an English walnut.

As lesser grades of this significant motion would probably be overlooked, its manifestation may prove to be not so very uncommon in cases of retro-mammary cyst.

Solid tumors projecting from the under-surface of the breast might, conceivably, in the absence of adhesions or exudative reaction give the same, roller-like glide.



## A CASE OF FOOT-AND-MOUTH DISEASE IN MAN.

By PAUL W. CLOUGH, M. D., Baltimore.

*(From the Medical Clinic of The Johns Hopkins Hospital.)*

The recent appearance of foot-and-mouth disease among cattle and hogs in this country is a matter of importance to physicians as well as to veterinarians, since the disease is occasionally transmitted from animals to man. As its appearance hitherto has been rare in the United States, and as the possibility of human infection has not generally been realized in this country, it seems desirable to put on record a description of a moderately severe typical case of the disease from the medical clinic of The Johns Hopkins Hospital. While it is not the intention to discuss in detail the epidemiology or the symptomatology, a brief outline of what has been learned from a study of the disease in animals is necessary for a clear understanding of its appearance in man.

For more than three centuries foot-and-mouth disease has been known in continental Europe, especially in Germany, Austria, Russia and the Balkans. It occurs in severe epizootics at intervals of from four to six years, causing heavy financial losses. During such an outbreak in Europe in 1911, in Germany alone cases were officially reported in approximately 3,300,000 cattle, 1,600,000 sheep, 2,500,000 hogs and 50,000 goats—about one-seventh of all the susceptible animals in the country.<sup>1</sup> In the intervals between the severe epizootics smaller numbers of sporadic cases occur. The United States has been relatively free from the disease. There was an extensive outbreak in 1870, and limited ones in 1880, 1884, 1902 and 1908. During the past year it has again appeared and has prevailed throughout most of the eastern states.

Of the domestic animals cattle are most susceptible to the disease.<sup>2</sup> Hogs, sheep and goats are somewhat less so. Much more rarely horses, dogs and cats are affected, and occasionally man. Rabbits, guinea-pigs and birds are only rarely infected, even by inoculation. Among susceptible animals the disease is highly contagious, attacking a large proportion of those exposed. In cattle the morbidity rate is often 40% and in some epidemics it has even been 95%.<sup>2</sup> Infection may be by direct contact, but it is most often indirect, by means of contaminated hay or bedding, stalls, common drinking-troughs, or pastures. Infected stock cars and stockyards play a very important rôle in disseminating the disease. Contaminated milk is a prolific source of infection in young animals.

The virus is present in the fluid of the vesicles wherever they occur. Susceptible animals, especially calves, may quite regularly be infected by applying fluid from a vesicle to an abraded mucous membrane or to the abraded skin of the foot or udder. This furnishes a reliable, though expensive method for the experimental study of the disease. The fluid of the

vesicle contains the virus in high concentration, 0.0002 cc. often sufficing to infect a calf.<sup>3</sup> It is present in the saliva, feces, urine or milk, whenever these secretions become contaminated with fluid from a ruptured vesicle.<sup>4</sup> After the healing of the ulcers which form when the vesicles rupture the contagion usually disappears;<sup>4</sup> but there is some epidemiological evidence in support of the view that animals occasionally carry contagion for some weeks after clinical recovery.<sup>2, 5</sup> The virus is present in high dilution in the circulating blood early in the disease, before the vesicles appear. Furthermore, the typical lesions of the mouth and feet develop after infection by intravenous, intraperitoneal or intramuscular injections,<sup>3</sup> and occasionally follow the feeding of gelatin capsules containing lymph.<sup>2</sup> The disease must therefore be regarded as a general systemic infection, and the usual distribution of the lesions in the mouth and on the feet must be due as much to a special susceptibility of these tissues to the virus as to the fact that these locations constitute the usual portal of entry of the infection.

All attempts to demonstrate or to cultivate the microorganism causing the disease have been unsuccessful. However, Loeffler and Frosch<sup>3</sup> in 1898 showed that the lymph from a vesicle did not lose its virulence after it was diluted 1 to 40 in water and then passed through a Berkefeld filter. The disease therefore is one of those that are caused by a filterable virus, and the causative agent is probably ultramicroscopic.

The virus is relatively non-resistant.<sup>3</sup> It is quickly destroyed by light, heat, drying and disinfectants. It dies out within 12 hours if the lymph is kept at body temperature. It is killed by heating for 30 minutes at 70° C., and usually, though according to Loeffler not always, at 60° C. Thorough pasteurization should therefore render the milk non-infectious; but to insure absolute safety from infection, milk from diseased animals, if used at all, should be boiled. The virus is fairly resistant if kept cool and moist. In this condition it clings very tenaciously to contaminated objects, and thorough disinfection is necessary to rid an infected district of contagion. Possibly some of the infections which have been regarded as indirect may have been due to direct contact with healthy carriers.

In cattle<sup>2</sup> the disease usually develops in from two to seven days after exposure, with slight fever, frequent pulse and loss of appetite. The mucous membranes of the mouth, lips, and

<sup>1</sup> Mohler, J.: Foot-and-mouth disease. Farmers' Bull. No. 666, U. S. Dept. Agric., 1915.

<sup>2</sup> Hutyra, F., and Marek, J.: Special pathology and therapeutics of the diseases of the domestic animals, Am. Ed., I, 328. Mohler & Eichorn, Chicago, 1914.

<sup>3</sup> Loeffler and Frosch: Berichte der Kommission zur Erforschung der Maul- und Klauenseuche bei dem Institut für Infektionskrankheiten in Berlin. Centralbl. f. Bacteriol., I Abt., 1898, XXIII, Orig., 371.

<sup>4</sup> Schütz: Impfversuche zum Schutze gegen die Maul- und Klauenseuche. Arch. f. Thierheilk., 1894, XX, 1.

<sup>5</sup> Loeffler: Die Schutzimpfung gegen die Maul- und Klauenseuche. Deutsche med. Wchnschr., 1905, XXXI, 1913.



often of the pharynx, become inflamed, deeply injected and very tender. The animals refuse all food. Salivation develops early, and because of the pain on swallowing, the saliva accumulates and drools from the mouth. The animals become listless and stand quietly unless forced to move. They rapidly become emaciated. The milk is greatly reduced in quantity and is often so changed in consistency and taste as to be unfit for use. After two or three days vesicles appear on the lips, gums, cheeks and upper jaw, attaining a diameter of 1 to 3 cm. The fluid is at first clear, but often becomes cloudy or purulent if secondary infection occurs. A little later vesicles usually appear on the feet, especially on the skin of the coronary band, on the heel and between the toes. When the feet are involved the animals become lame and may be unable to walk, or even to stand. Lesions frequently occur on the udder. The mucous membrane of the milk ducts may be involved, and even the parenchyma of the gland. In such cases the milk is highly infectious; it is not infectious if the udder is free from disease.<sup>9</sup> After one to three days the vesicles rupture, leaving superficial, deeply injected, very tender ulcers, which gradually heal unless secondary infection takes place. This frequently occurs in the ulcers on the feet, and if neglected often results in the formation of abscesses, which may burrow deeply and lead to loss of hoofs, serious damage to the joints, and even to death from pyæmia. Recovery, however, is the rule.

In adult animals the average mortality is only about one-half of one per cent.<sup>2</sup> In some epidemics, however, the disease appears in a malignant form, the mortality reaching 50%, or even a much higher figure. Death in such cases may be apoplectiform, due to a degeneration of the myocardium, or may result from a bronchopneumonia. In calves there is often a severe gastro-enteritis, and the mortality is high—about 20% or over.

Animals which survive the infection acquire some immunity, but only for a limited period. Recurrences are uncommon during the first year, but in some instances have occurred within six weeks.<sup>7</sup> It is possible to immunize animals artificially,<sup>8</sup> either actively by vaccination (result very uncertain) or passively by injections of immune serum; or by a combination of the two methods. But no method of any practical value has been devised, for the results are uncertain, the more effective procedures are dangerous, the immunity when obtained is of short duration, and all methods at hand are very expensive.

The occurrence of the disease in man has been recognized for more than two centuries. A large number of reported cases of human infection have been collected by Bussenius and Siegel.<sup>9</sup> Their report quite exhaustively covers the literature from 1695 to 1896. While some of the reported cases may be

questioned, others are of undoubted authenticity and demonstrate the frequency of human infection. The apparent rarity of the disease in man is due in part to the facts that it usually runs a mild course and that it occurs most frequently in the poorer class of peasants, who rarely consult a physician for minor ailments. Most of the recorded cases have been observed by veterinarians and reported in foreign veterinary journals, which are seldom read by physicians and which are practically inaccessible in this country. The disease occurs in man in regions in which it is widespread among cattle. That it is not rare in such circumstances is shown by the fact that from 1887 to 1894 six hundred cases in man were officially reported in Germany.<sup>10</sup> It may be contracted by direct contact with diseased animals,<sup>11</sup> or by ingestion of infected milk or cream,<sup>12</sup> butter<sup>13 14</sup> or cheese.<sup>15</sup> The use of infected milk has given rise to extensive epidemics in which entire families, and even communities have been attacked.<sup>16</sup> Children are especially susceptible. The possibility of human infection following the use of contaminated milk was demonstrated experimentally by Hertwig in 1834.<sup>17</sup> Hertwig and two of his assistants each drank a quart of milk from a cow known to be infected. All three developed a typical attack of the disease. According to Demme<sup>18</sup> milk is infectious even when used in coffee. The sporadic cases occur most frequently in stablemen, butchers, milkers, and others who come into direct contact with diseased animals. The infection is probably transmitted through abrasions of the skin of the hands or of the mucous membrane of the nose and mouth.

The symptoms of the disease as described in man<sup>18 19 20</sup> are very similar to those observed in cattle. In the majority of cases it takes a mild form. After an incubation period of two to five, or even ten days, the disease usually sets in with fever of moderate severity, some general malaise and prostration, and a feeling of dryness and burning in the mouth. The

<sup>10</sup> Amtliche Mittheilungen der Jahresberichte über die Verbreitung von Thierseuchen im deutschen Reiche. Collected and cited by Bussenius and Siegel.<sup>9</sup>

<sup>11</sup> Nowikow: Arch. f. vet. Med., 1893, II, 261. Cited by Bussenius and Siegel.<sup>9</sup> (Original reference not accessible.)

<sup>12</sup> Hertwig: Uebertragung thierischer Ansteckungsstoffe auf Mensch. Berl. med. Ztg., 1834, Nrn. 48-50, S. 225. Cited by Bussenius and Siegel.<sup>9</sup> (Original reference not accessible.)

<sup>13</sup> Fröhner: Ein Fall von Uebertragung der Aphthenseuche (Maul- und Klauenseuche) vom Rinde auf den Menschen durch Süßbutter. Ztschr. f. Fleisch- u. Milchhyg., 1891, I, 55.

<sup>14</sup> Lorenz: Uebertragung der Aphthenseuche auf den Menschen durch Genuss von Süßrahmbutter. *Ibid.*, 1893, III, 176.

<sup>15</sup> Schneider, J.: Neueste Erfahrungen über die Maul- und Klauenseuche des Rindviehs, des Schafe, Schweine, etc. Ann. d. Staatsarzn., 1840, V, 1.

<sup>16</sup> Siegel. Die Mundseuche des Menschen (stomatitis epidemica), deren Identität mit der Maul- und Klauenseuche der Haus-thiere, etc. Deutsche med. Wehnschr., 1891, XVII, 1328.

<sup>17</sup> Demme, O.: Ueber die Uebertragung der Maul- und Klauenseuche durch die Milch. Wien. med. Bl., 1883, VI, 8.

<sup>18</sup> Glaister, J.: A case of foot-and-mouth disease in the human subject. Lancet, Lond., 1896, II, 872.

<sup>19</sup> Koránji, F.: Die Maul- und Klauenseuche. Nothnagel's Speziel. Path. u. Ther., 1897, V, 5 Th., I Abt., 137-150.

<sup>20</sup> Boggs, T. R.: Foot-and-mouth disease. Osler's Modern Med., Ed. 2, 1913, I, 1025.

<sup>9</sup> Nocard: Rev. gén. de méd. vét., Toulouse, 1903, I, 369. Cited by Koránji (19). (Original reference not accessible.)

<sup>7</sup> Strebel. Cited by Caspar (8). (Original reference not accessible.)

<sup>8</sup> Caspar, M.: Immunität bei Maul- und Klauenseuche. Kolle and Wassermann's Handb. d. path. Mikroorg., Aufl. II, 1913, VI, 214.

<sup>9</sup> Bussenius and Siegel: Kann die Maul- und Klauenseuche des Viehes auf den Menschen übertragen werden? Ztschr. f. klin. Med., 1897, XXXII, 147.





FIG. 1.—Shows the appearance of the hand on the seventh day. Note the blotchy erythematous areas surrounding the flat papules, four of which are capped by unruptured vesicles; also in two areas, the shallow excoriations following rupture of the vesicles.









FIG. 2.—Shows the vesicles on the lips and tongue on the seventh day. Note the intense dusky red color of the mucous membrane.









FIG. 3.—Shows the appearance of the foot on about the tenth day, after desquamation had begun. Note the small reddish-brown areas of fading purpura over the toes where desquamation had not yet occurred.







mucous membrane of the lips, cheeks and gums becomes deeply injected and sore. Salivation develops. After two or three days small vesicles appear at these locations, and also on the edges and ventral surface of the tongue, and in the pharynx; more rarely also on the hard palate, in the nose, on the conjunctiva, or on the skin adjacent to these regions. With the appearance of the exanthem the fever and the constitutional disturbances usually subside. The vesicles attain a diameter of 2 to 10 mm., though adjacent ones may coalesce to form larger blebs. They contain a clear or slightly cloudy fluid, which may subsequently become purulent. There is usually swelling of the tongue and lips, sometimes of the nose, and even of the entire face. After two or three days the vesicles rupture, leaving superficial, deeply injected, very tender ulcers, which heal quickly and without scarring unless secondary infection occurs. There is moderate swelling of the regional lymph glands, and often of the salivary glands. Until healing takes place the burning, pain and tenderness in the mouth are intense. There is profuse salivation and great pain on eating, speaking or swallowing.

In the mild forms, which constitute the great majority of all human cases, there may be no symptoms other than the appearance of a few vesicles in the mouth. In the more severe cases, usually shortly after the appearance of the vesicles in the mouth, similar vesicles appear on the skin of the hands and feet. The hands are most often affected, and the eruption is rarely limited to them. The lesions are most numerous on the finger-tips, on the volar side of the fingers and at the base of the nails. Less often they occur at the base of the fingers, on the middle of the hand or the arms. Swelling, itching and burning of the fingers and toes often precede the appearance of the eruption. If the feet are involved, the vesicles usually occur on the toes and heel. They occasionally occur on the genitals and about the nipples. Very rarely they may be disseminated over the whole body. They rupture and heal much as do those in the mouth. Secondary infection of the ulcers on the toes or fingers may lead to loss of the nails. In severe cases petechiæ have been described.<sup>16 21</sup>

In children, and less often in adults, there may be more serious general symptoms, with chills, high fever, colicky abdominal pain, nausea, vomiting, and diarrhoea with bloody stools. Such cases may end fatally, as may those in which serious secondary infections occur. During a severe epidemic near Berlin, reported by Siegel,<sup>16</sup> out of a population of 9,000 it was estimated that two-thirds contracted the disease during a period of three years. There were 36 deaths attributed to the infection, 15 in children and 21 in adults.

Proof of the identity of the disease in man and animals has been furnished by Schautyr<sup>22</sup> and by Bertarelli,<sup>23</sup> who each

<sup>16</sup> Boas: Maul- und Klauenseuche beim Menschen. Deutsche med. Wehnschr., 1893, XIX, 972.

<sup>22</sup> Schautyr: Beiträge zur Lehre der Maul- und Klauenseuche beim Menschen. Arch. f. vet. Med., 1893, II, 87. Cited by Koránji.<sup>19</sup> (Original reference not accessible.)

<sup>23</sup> Bertarelli: Uebertragung der Maul- und Klauenseuche auf den Menschen und Wiederimpfung der menschlichen Krankheit

transmitted the disease to calves by inoculation with a virus obtained from a human subject.

The case here reported corresponds closely in its essential features to the published descriptions of the disease:

C. L., white, male, medical student, aged 20. Admitted December 26, 1914.

*Complaint.* Sore throat.

*Family History.* Unimportant.

*Past History.* General health excellent. Measles, mumps and scarlet fever in childhood. Received a prophylactic dose of diphtheria antitoxin after scarlet fever. No other acute illnesses. No venereal infection. Habitual smoker.

Patient's home was in Nebraska, but from October 1, 1914, he had been in regular attendance at the Johns Hopkins Medical School, and had not been in the country, or out of the city, until December 24, one day before the onset of the present illness, when he had gone to Washington, D. C. He had not been in contact with any animals. He had drunk no milk, but had eaten butter and had used cream with coffee, etc. No case of a similar nature was known in his boarding house or in the neighborhood.

*Present Illness.* Onset December 25, the day before admission, with burning and soreness of the feet. The following morning he noticed a dry taste in his mouth, "like alum"; this rapidly increased to a painful, burning sensation, and the throat became very sore. The pain in the toes increased, and they became tender, red, swollen and numb. There were no other symptoms, and no general discomfort.

*Physical Examination.* On admission, the night of December 26. Robust, well-nourished, healthy-looking man. Temperature 99.8°; pulse 100; respirations 20. No especial discomfort. Face very slightly swollen. No eruption on skin. Glands palpable at the angle of the jaws. The chest and abdomen showed nothing of importance. The spleen was not felt, though it became palpable on the tenth day.

The tongue was moist and coated. The mucous membrane of the mouth was rather dry and red. The tonsils were only slightly enlarged. The pharynx and tonsils were deeply injected, as were also the posterior portion of the soft palate, and the cheeks, especially along the line of closure of the teeth, where there were several small, slightly elevated, yellowish areas of exudate, 1 to 3 mm. in diameter. The posterior pharyngeal wall and the tonsils were covered with a thin layer of greyish muco-purulent exudate, which was very readily removed with a swab. There were no ulcerations.

The toes and feet were swollen as far back as the metatarsophalangeal joints. The skin was tense, deep red and tender. Tingling and intense itching were complained of.

Smears from the throat showed no fusiform bacilli or spirilla. There were a few bacilli suggestively beaded at the ends. Diphtheria antitoxin (5000 units) was accordingly given, but cultures later proved to be negative for diphtheria.

By the third day (December 27) the inflammatory process in the mouth had extended very markedly. The inner surfaces of the cheeks and lips were involved; also the ventral surface and lateral margins of the tongue, and the grooves between the tongue and the gums and between the gums and the cheeks. The mucous membrane was intensely red, raw and very sore. There were numerous small, slightly elevated, yellowish areas, 2 to 5 mm. in diameter, which in places coalesced to form areas 1 to 2 cm. in diameter. Marked salivation developed. By the fourth day the process had extended until practically all the visible mucous membrane had become involved, including the hard palate and

auf die Rinder. Centralbl. f. Bakteriologie, I. Abt., 1907, XLV, Orig., 628.







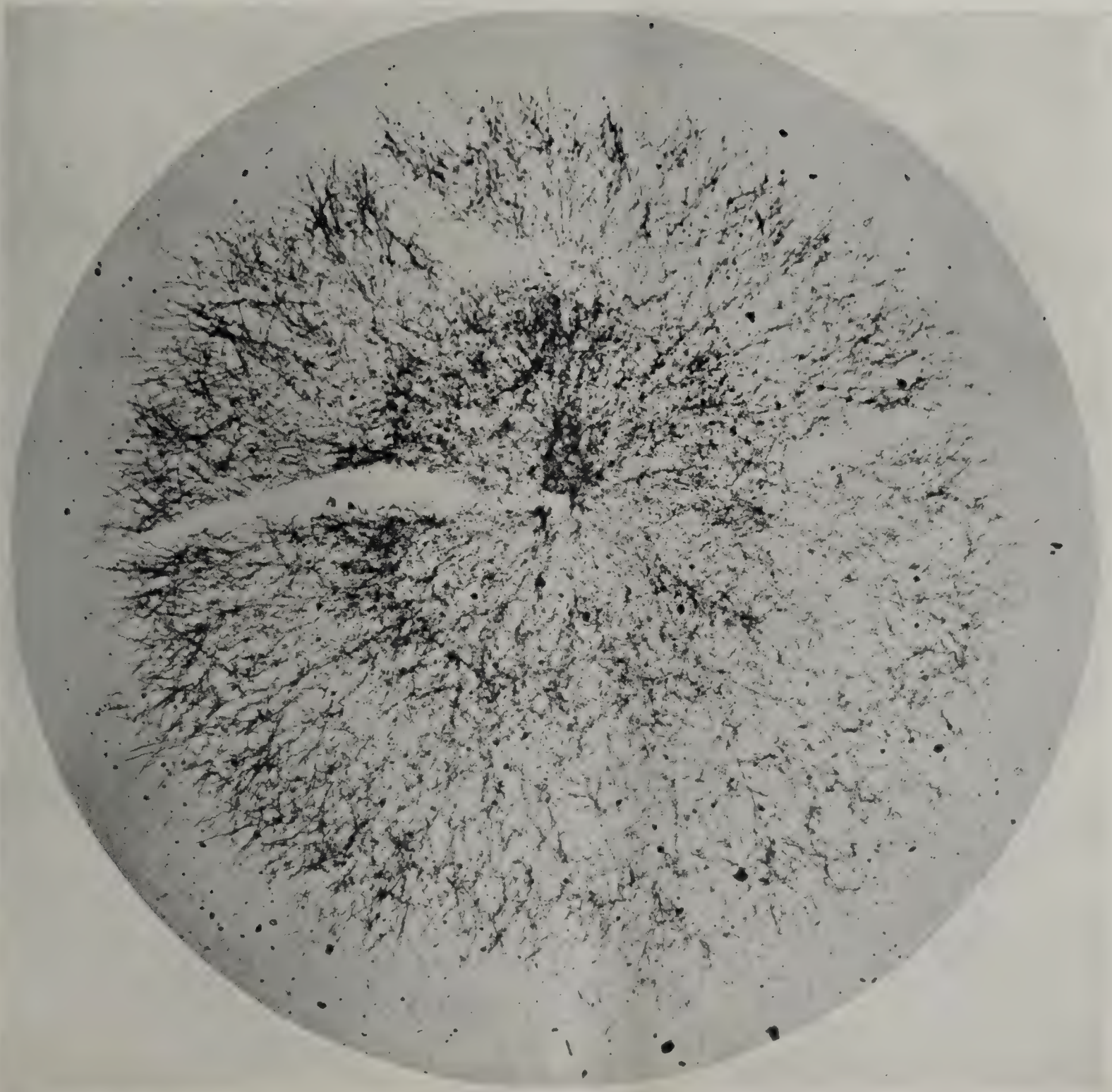


FIG. 5.—Trichophyton violaceum, 8-day gelatin. Crystal-violet stain. ( $\times 300$  diam.)

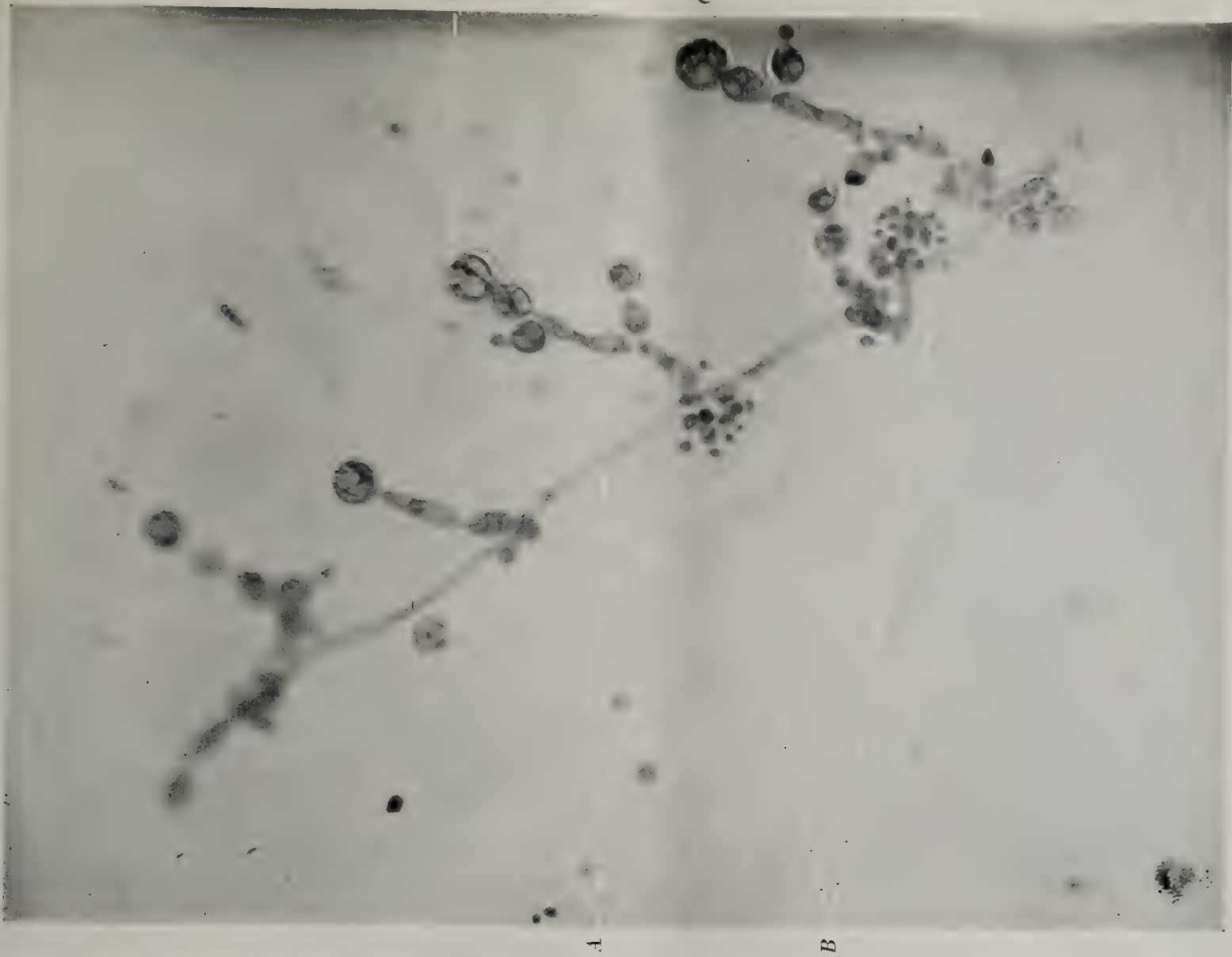


FIG. 6.—Monilia(?). Author's case. Section from 8-day gelatin stab, fuchsin stain. ( $\times 1000$  diam.) Hypha (A) with ordinary spores (B) and chlamydo spores (C) on same thread.







lateralward from the stab. When the development has reached the desired point, 10% formalin is poured on the top of the culture and the gelatin is hardened *in situ*. After 48 hours, the tube may be cracked and the glass peeled away from the gelatin, which is of a firm, somewhat rubbery consistency. Selected blocks are then cut from this culture and sections made with the freezing microtome. Where sections of the surface growth are desired, the culture is hardened as above, and the supernatant formalin is poured off and replaced by melted gelatin. After cooling, this top layer is also treated with formalin and, when hardened, blocks may be cut, including the surface growth in the direction desired. The thickness of the sections should be varied with the dimensions of the filaments and reproductive organs under consideration. Our sections have been from 10 to 25 microns.

These sections give an admirable picture of the relation of the filaments to the stab and of the various methods of sporulation developed in the culture. The threads, spores and other reproductive structures are held absolutely fixed in the relations in which they have developed. The sections may be studied unstained, including dark field illumination, or they may be stained in various ways. The aqueous methods of staining and of differentiation have seemed to us to be the most rapid and to produce the least distortion. We have employed for this purpose dilute carbol-fuchsin, one to thirty (of the standard stain for tubercle bacilli), staining from 12 to 24 hours. The heavily stained sections are then differentiated rapidly in a saturated citric acid solution. When the desired decolorization is reached, the sections are washed in water, mounted on a clean slide, drained and allowed to dry in the air without blotting. When thoroughly dry they are rapidly cleared in xylol and mounted in balsam. In order to retain the stain in the filaments the decolorization must be stopped while the medium is still distinctly pink. This stain is of especial value for the details of cell structure under high powers. For the study of the general morphology and the spatial relations of the filaments and reproductive organs, a stain which allows of more complete decolorization of the medium is desirable. The sharper contrast thus obtained results in a schematic picture of the growth. For this purpose Victoria Blue (at the suggestion of Maj. B. K. Ashford) is used (one part of a saturated alcoholic solution to 50 parts of distilled water). The sections are stained overnight, mordanted for one to two minutes in Lugol's solution, washed in water, and decolorized in 95% alcohol. The decolorization should be frequently interrupted by transferring into distilled water, where the depth of color retained may be observed. When the medium shows only a faint blue tinge, in contrast to the deeply stained organism,

the sections are floated on slides and air-dried. Then after clearing in xylol they are mounted in balsam. Such sections show the organisms stained deeply blue to bluish-black; the filaments and cells being specially sharp, while the internal structure is not so well differentiated. These preparations are particularly adapted to photographic reproduction.

The crucial advantage of these methods is the fact that the spatial relations of the different parts of the organisms are exactly preserved; a point which cannot be overestimated as an aid in the classification of the organisms. The gelatin cultures also lend themselves admirably to the study of the gross morphology of filament production, as is illustrated in the accompanying photographs.

Furthermore, we have found that organisms which do not grow at room temperatures (such as are alone suitable for gelatin cultures) may be studied in a similar manner by using a medium composed of 1% agar-agar and 7% gelatin, carefully cleared as in preparing the gelatin medium. This will stand up in the thermostat and in our hands has given excellent sections, which stain quite as well as the gelatin, but which require more care in handling as they are more friable.

The medical and technical books on mycology, for the most part, make no mention of such methods of study, and it is our impression that the neglect of these methods adds to the difficulty in recognizing the type forms of these organisms. Morphological details are at present the main dependence in classification, and the only hope of satisfactory identification of a given organism may lie in the persistent use of rich culture media and the study of the organism morphologically, at various stages of its development. Organisms which in the early period after isolation present only a small yeast-like form, after repeated transfers and changes of media may develop one or more characteristic methods of reproduction; and until these are found and properly identified the classification of the organisms is incomplete. The wide variation in cultural characteristics, especially in the reactions produced in carbohydrate media, makes identification by such methods difficult and confusing. The same strain of an organism in culture often exhibits marked changes in its reaction toward specific carbohydrates.

It is to be hoped that this morphological method may be more widely employed and lead to a better and clearer classification of these very confusing groups.

The best of our micro-photographs we owe to the unfailing kindness of Prof. Erwin F. Smith, of Washington, D. C.

We wish especially to express our thanks to Doctors M. C. Winternitz and W. W. Ford, for their assistance in furnishing laboratory facilities.

## JOHNS HOPKINS HOSPITAL BULLETIN.

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A STUDY OF THE FERMENTS AND ANTIFERMENTS OF THE BODY  
AND THEIR RELATION TO CERTAIN DISEASES.\*

By JAS. W. JOBLING, M. D., AND WILLIAM F. PETERSEN, M. D.

(From the Department of Pathology, Vanderbilt University Medical School, Nashville, Tenn.)

During the past few years much work has been done to prove that immunity from infection is due to the presence of specific ferments. Vaughan<sup>1</sup> was able to obtain toxic substances by hydrolyzing proteins with alcoholic potash; he therefore concluded that intoxications accompanying infections are due to the production of poisons liberated through the action of specific proteolytic ferments. More recently Abderhalden,<sup>2</sup> by means of the polariscope and of dialyzing membranes, has elaborated a technic whereby he claims that he can demonstrate the presence of specific ferments in the blood of pregnant women which are capable of splitting the placental protein. The work of these two authors and the views which they advance render it necessary to determine if the body can generate ferments which will attack only certain native proteins.

In order to determine if the ferments of the body are capable of producing toxic substances from native proteins, one of us (Jobling) with Strouse<sup>3</sup> studied the cleavage products obtained by the action of leucoprotease on various proteins. Opie,<sup>4</sup> Müller<sup>5</sup> and others, had already shown that leucocytes contain very active ferments. We found that these cleavage products are toxic and that the toxicity is almost wholly confined to the primary proteose fraction.

Similar results were obtained by treating bacterial proteins with leucoprotease. It was found that the toxic substance is bound up with the native protein and cannot be separated from it excepting through the action of ferments. All those means by which the native bacterial protein is removed from a freshly prepared solution, leave a comparatively non-toxic filtrate, though boiling a solution made slightly alkaline to prevent coagulation does not destroy the toxicity. On the other hand, toxic substances free from native protein may be obtained through the action of leucoprotease, and they are also present in the primary proteose fraction. These results do not necessarily mean that there are no true secretory toxins, but show that toxic substances may be produced by hydration of the bacterial proteins.

ANTIFERMENTS.

With the knowledge that toxic substances may be derived from proteins as a result of the action of proteolytic ferments normally present in the body, we deemed it necessary to make a more careful study of the substances which inhibit the action of proteases.<sup>6</sup>

In our first experiments we studied the ferment-inhibiting agents contained in tubercle bacilli and in tuberculous caseous material. We studied caseous material because of the fact

that its production in tuberculosis must be partly due to the presence of substances which inhibit the action of the ferments set free as a result of the disintegration of the cells.

In these experiments we found that suspensions of the ether and alcoholic extracts of tubercle bacilli were inactive as anti-ferments, but that the soaps prepared by saponifying the extracts with sodium alcoholate were very active. The inactivity of the unsaponified extracts in sodium chloride solution is probably due to the coarseness of the suspension.

Having found that soaps prepared in this manner were actively antitryptic, we then tested them to see if their activity was due to their degree of unsaturation. The fatty acids were treated by the ether-lead soap method, and the ether

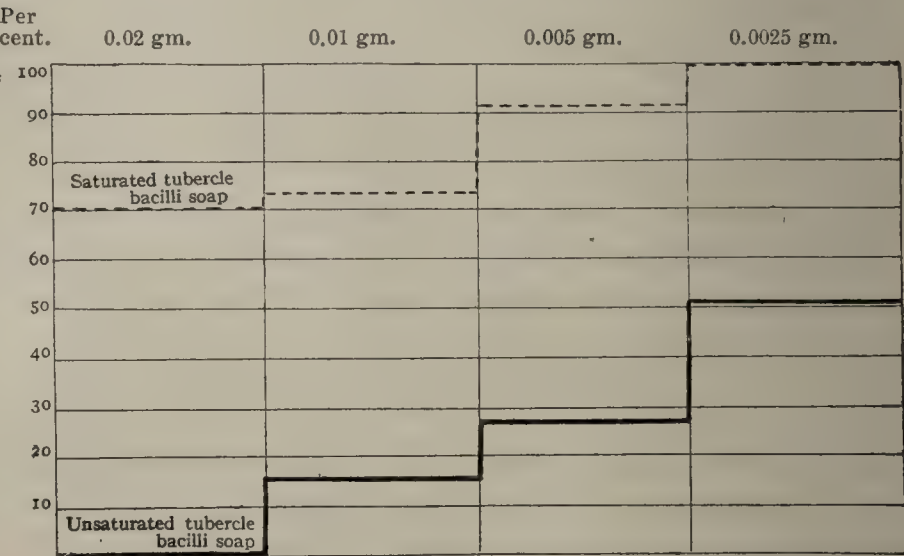


CHART 1.—Effect of saturated and unsaturated soaps of tubercle bacilli on tryptic digestion.

soluble fraction was tested for its ferment-inhibiting action. This method, of course, does not give a complete separation of the saturated and unsaturated fatty acids, but the separation was sufficient to prove to us that the unsaturated fatty acids are the active agents. It was further found that saturation of the unsaturated carbon bonds with iodine, or with hydrogen peroxide, would destroy their antiferment activity.

Similar results were obtained with the caseous material from tuberculous lymph-glands and from caseous pneumonia. The ferment-inhibiting substances, the esters of the unsaturated fatty acids, were found in all material examined, but in relatively small amounts when the caseous material had been secondarily infected. This is probably due to the dilution and washing out of the esters.

These results shed considerable light on the action of iodides in tuberculosis. Tubercles and caseous areas may be present in the lung, but unless they open into the air passages tubercle bacilli may be absent in the sputum. If iodides are now given the caseous matter begins to soften, and is more likely to rupture into the bronchi, and the bacilli are then discharged in the sputum.

\* Read before The Johns Hopkins Hospital Medical Society, February 15, 1915.



The sudden discharge of the softened caseous material into the bronchi as a result of the action of the iodine, would also explain the occurrence of hemorrhages, as it would leave unsupported any blood-vessels traversing the mass whose walls had been involved in the tuberculous process to a degree that would render them unable to withstand the blood pressure without some outside support. We must also bear in mind the possibility that with the softening and absorption of these caseous areas, the tubercle bacilli may be disseminated.

#### FERMENT-INHIBITING ACTION OF SOAPS.

Having shown that soaps of the unsaturated fatty acids obtained from tubercle bacilli and tuberculous caseous material inhibit the action of trypsin and leucoprotease, we thought it necessary to determine if other unsaturated fatty acids possessed the same property. In order to obtain some information on this point we prepared soaps from oils known to contain a large number of unsaturated fatty acids. For this purpose we used linseed oil, hempseed oil, castor oil, olive oil, croton oil and cod-liver oil, and found that the activity of these soaps as ferment-inhibiting agents is dependent upon the degree of the unsaturation of the fatty acids, and is in proportion to their iodine value. The most active soaps were obtained from tubercle bacilli.

#### SERUM ANTITRYPSIN.

Having obtained some definite information concerning the nature of the ferment-inhibiting substances present in tubercle

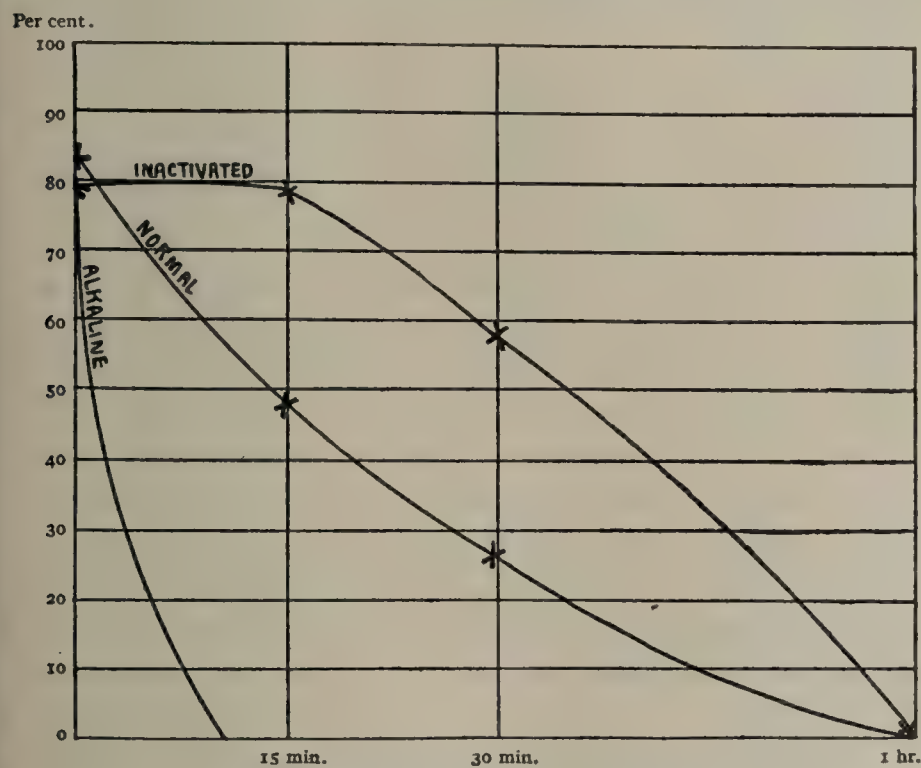


CHART 2.—Rate of removal of serum antitrypsin in normal, inactivated, and alkalinized serum at 37° C., when treated with chloroform.

bacilli and in tuberculous caseous material, we next turned our attention to the so-called antitrypsin of the blood.<sup>7</sup> We wished to see if this action of sera was due to the same agent.

Considerable work has been done by Schwartz,<sup>8</sup> Sugimoto,<sup>9</sup> Meyer<sup>10</sup> and Kirchheim<sup>11</sup> with lipid solvents in order to show the relation between the lipoids of the serum and antitrypsin,

but with contradictory results. The experiments were made with fresh serum from dogs, human beings, guinea-pigs and rabbits. We found that the antitryptic action became almost wholly lost in sera extracted several days at room temperature with chloroform or ether, and was wholly lost when they were incubated with chloroform at 37° C., for 60 minutes.

These experiments have been repeated and similar results have been obtained each time. It is necessary to shake the mixtures of chloroform and ether frequently, and at least twice as much solvent as serum should be used, otherwise the inhibiting action of the serum is not removed.

The chloroform and ether does not destroy the antitrypsin, as it can be recovered from the solvents almost quantitatively by appropriate means. A large portion of the anti-ferment action may be destroyed by incubating the serum over night with iodine and potassium iodide. This is due to the saturation of the unsaturated carbon bonds.

It is well known that the antitryptic action of the serum is destroyed if heated for 30 minutes at 70° C. This also occurs when the mixtures of the unsaturated soaps with protein substances are treated in the same manner. It is difficult to explain why this occurs. Thinking that it might be due to the coagulation of the proteins, we made protein-soap mixtures strongly alkaline with sodium hydrate and heated them to 70° C., for 30 minutes. They were then neutralized, and tested, and found to be still active as anti-ferments. As yet we have been unable to find any satisfactory explanation of this phenomenon. The iodine values of the heated and unheated mixtures are the same, so we must assume that the combination formed is one which is readily dissociated.

#### SEROTOXINS.

In view of the fact that many sera contain proteolytic ferments, we made experiments to determine whether such sera would become toxic for animals of the same species if the anti-ferments were removed.<sup>12</sup> The experiments were based on the idea that the ferments would act upon the exposed serum proteins.

In order to remove the anti-ferment, guinea-pig serum was incubated over night with two volumes of chloroform. It was then centrifuged and the clear serum filtered through coarse filter paper until the chloroform in solution had evaporated. It was found that serum of guinea-pigs treated in this manner was toxic for other guinea-pigs in doses of 0.003 cc. to 0.01 cc. per gram weight. The symptoms and post-mortem findings were similar to those observed in anaphylaxis. Subsequent experiments conducted with oxidizing agents such as free iodine gave similar results.

When the chloroform-serum mixture is incubated at 37° C., the serum becomes most toxic after 24 hours, and begins to lose its toxicity at the end of 48 hours. In some experiments, though, we observed that the toxicity reached its maximum within from 8 to 12 hours. This depends entirely upon the rate of removal of the protective lipid substances. The increase in the toxicity of the serum runs almost parallel with the increase of non-coagulable nitrogen.



We have already shown that the toxic fraction of the protein cleavage products lies in the primary proteose fraction, and that the continual action of the ferment soon renders it non-toxic owing to the further cleavage. The decrease in toxicity noted in the above experiments is probably due to the same cause. Freshly prepared serotoxins show no increase in non-coagulable nitrogen, and toxic split-products cannot be isolated by fractionating the serum with ammonium sulphate. These results indicate that exposed serum-proteins are split to toxic substances when injected into the circulation of animals. We have termed the poison developed in this manner, "serotoxin."

We observed during the course of the work that when excessive doses of the serotoxins were given the post-mortem revealed extensive intra-vascular coagulation of the blood. On the other hand, minimal doses appeared to lengthen the

Cc. per gm.  
of weight of  
guinea-pig.

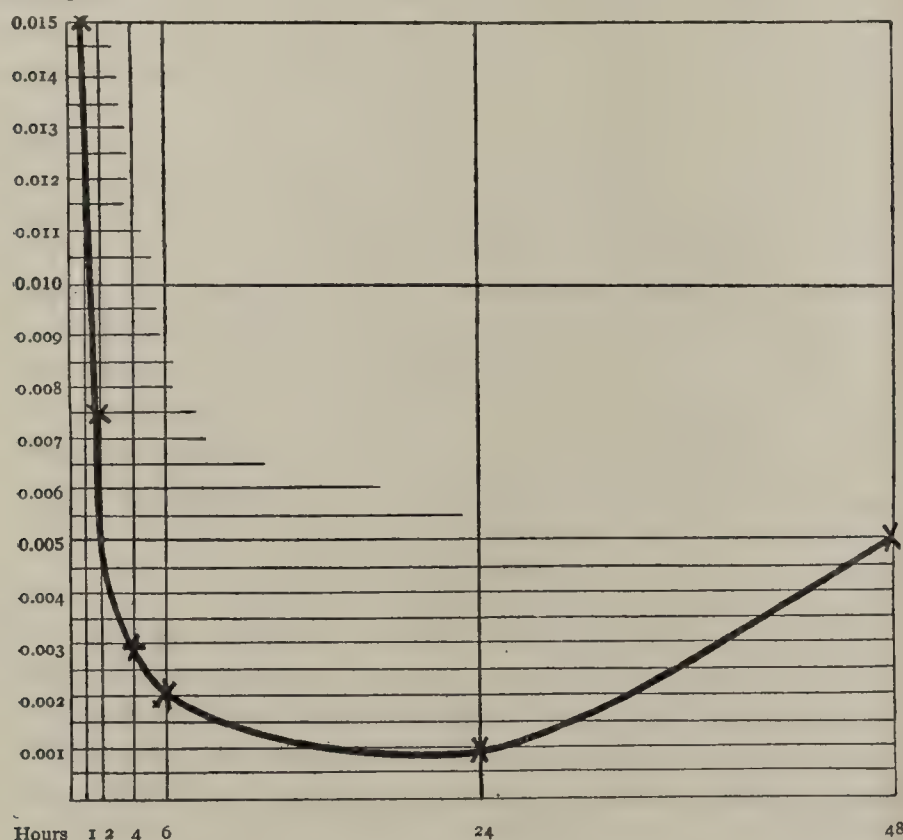


CHART 3.—Curve showing the increase of toxicity of guinea-pig serum treated with chloroform at 37° C. Minimum lethal dose in cc. per gm. of weight.

coagulation time. This caused us to consider the possibility of emboli being the cause of death, even when small doses were given. In order to rule out this factor, we gave a series of guinea-pigs large amounts of hirudin intravenously five minutes before injecting the toxin, and then gave large and small amounts of the toxic sera. There were no evidences of intravascular coagulation in the animals that died as a result of the action of the toxin. We shall not attempt to explain why intravascular coagulation should follow the intravenous injection of these substances, but wish to state that similar results are obtained following the intravenous injection of the soaps of the saturated and the unsaturated fatty acids.

If we are correct in assuming that the toxicity of the serum is due to the removal of the protective substances, then by returning these extracted substances the serum should become

non-toxic. It is practically impossible to restore the lipoids to the serum in the fine state of dispersion in which they are active, and so they were saponified and used in the form of soaps. By the use of this method it was found that we could neutralize the toxicity of freshly prepared serotoxin. If, on the other hand, we used the serotoxin prepared by extracting the serum for 24 hours at 37° C., the toxin could not be neutralized. This indicates that the soap is of value only in so far as it prevents the formation of the toxin, and that it cannot neutralize those which are present at the time the soap is added.

Freshly prepared sera are much more toxic for animals in which the normal antitrypsin has been reduced by painting the shaved skin with tincture of iodine. The antitrypsin of the serum of guinea pigs treated in this manner is greatly decreased, and they succumb when given one-third to one-fifth the amount of serum necessary to kill a normal animal.

#### ANAPHYLATOXIN.

The similarity of the results obtained by us with serotoxin and those obtained by Friedberger,<sup>13</sup> Doerr,<sup>14</sup> and others with the so-called anaphylatoxins, suggested to us the possibility that the toxins obtained by treating bacteria with fresh guinea-pig serum might also be derived from the serum instead of from the bacteria, as is generally supposed. This view is confirmed by the work of Friedemann,<sup>15</sup> Ströbel,<sup>16</sup> Bordet,<sup>17</sup> and other investigators, who have obtained preparations toxic for guinea-pigs by treating fresh guinea-pig serum with kaolin, agar, Kieselguhr, starch, waxes and fats from bacilli, besides the true antigens, which last need not be specific, for they are still effective after boiling. It has also been shown that the complement is not essential, for toxic sera can be produced from inactivated serum, although not with the same regularity as from active serum.

Briefly, we found that those agents, which are most effective in making the guinea-pig serum toxic, are also most effective in removing the antitrypsin; in almost every instance the toxicity bore a definite relation to the degree of the removal of the anti-ferments.<sup>18</sup>

Most authors working on this subject believe the toxicity of anaphylatoxins to be due to the toxins derived from the bacterial bodies; hence a large portion of our work was done with bacteria. We wished to determine, first, if bacteria adsorbed such anti-ferments and thus exposed the serum proteins to the action of ferments and, secondly, if there was a loss of bacterial nitrogen as a result of the treatment. As a result of these experiments we found that the bacteria adsorb the anti-ferments as readily as kaolin, agar, starch, etc., and that they become much more resistant to the action of trypsin.

In most of these experiments in which known quantities of bacteria, as determined by the total nitrogen present in the emulsion, were used, we found that the bacteria treated with serum were not destroyed. In fact the total nitrogen in the bacteria thrown down in the centrifuge, and then washed thoroughly, was as high if not higher than in those treated with salt solution.



Dold<sup>19</sup> observed that anaphylatoxins could not be obtained with bacteria which had been treated with oils or with cholesterol. We confirmed the work of Dold, and believe that the results are due to the saturation of the bacteria with the oils or cholesterol to such a degree that they are unable to take up the lipoids of the serum. In confirmation of this view we observed that serum mixed with bacteria which had been treated in this manner does not lose its antiferment as it does when mixed with untreated bacteria. Further, we found here, as in the preparation of serotoxin, that the toxicity of the product bears a definite relation to the degree of adsorption of the antiferment. These results would seem then to prove definitely that the toxicity of the anaphylatoxins is due to the presence of cleavage products derived from the proteins of the serum, and not from the bacteria.

#### LIPIDS AND SERUM ANTITRYPSIN IN ANAPHYLAXIS.

Rusznjak,<sup>20</sup> Pfeiffer and Jarisch<sup>21</sup> observed that the serum antitrypsin is increased following the recovery from anaphylactic shock; and we observed that the same thing occurred after a sublethal dose of serotoxin. We also found that animals recovering after having received an intravenous injection of serotoxin are able to withstand two or three times the minimum toxic dose if given within 24 hours. These results led us to consider the possibility of the refractory period following anaphylactic shock being due partially to this factor.<sup>22</sup>

We made a series of experiments on animals in which the antitrypsin had been increased to see if they could be made more resistant to a second dose of the specific protein used to sensitize them. The antitryptic strength was increased by giving the animals subcutaneous injections of serum lipoids dissolved in olive oil, and of fats prepared from egg-yolk. The guinea-pigs were sensitized with horse serum. The results of the experiments show that animals, whose antitryptic strength has been raised by injection of these lipoidal substances 24 hours previous to receiving the second and intoxicating dose, can withstand at least twice the minimum lethal dose of the antigen.

The knowledge that lipoids within certain limits may inhibit anaphylactic shock, caused us to study the toxicity of lipoid-free serum albumin, as a specific antigen in anaphylaxis. We found that the lipoid-free albumin used for the second and intoxicating dose was about four times as toxic as the unextracted albumin.

We have already mentioned that the lipoids of the serum when saponified will neutralize the toxicity of freshly prepared serotoxin, and this was also observed to be true of the second and intoxicating dose of serum albumin in anaphylaxis. It was found that sodium oleate can neutralize from five to six times the amount of serum albumin required to produce anaphylactic shock, but does not protect against the straight serum. Care must be taken in the use of sodium oleate, as in larger amounts it also will cause death with most of the phenomena observed in anaphylaxis.

#### BACTERIAL ANTIFERMENT.<sup>23</sup>

The resistance of bacteria to enzyme action, because of its importance as a factor in the defense of the invading organism against the destructive agencies of the host, has interested several observers, among them, Kruse,<sup>24</sup> Fermi,<sup>25</sup> Kantorwicz<sup>26</sup> and Weinkoff.<sup>27</sup>

The older conception that bacteria resisted digestion because of some vital property had to be discarded when it was found that organisms killed by chloroform, toluol, carbolic acid, etc., seemed to resist digestion as well as viable bacteria. It has so far been the implied idea that since bacteria contain protein, such protein should be an available substrate for enzyme action, in other words, that the bacterial cell represented a freely exposed mass of protein. In dealing with an intact cell there are, however, certain factors which indicate that this position is untenable.

Bacteria contain fats and lipoids in varying amounts, which, because of their marked effect on surface tension, would for purely physical reasons tend to become concentrated at the periphery of the colloidal system such as the bacterial protoplasm. Czapek<sup>28</sup> states that if the limiting membrane is similar to that present in plant cells it would consist chiefly of lipoidal substances.

With or without a morphologically distinct limiting membrane we can reasonably assume that the external surface of the bacterial cell is potentially lipoidal. In this connection it is interesting to recall the observation of Metchnikoff. Metchnikoff noted that the intestinal tract of the larva of moths was free from bacteria, and reasoned that this absence of intestinal flora must have some connection with the nature of the enzymes secreted in the gastro-intestinal tract. He calls attention to the fact that these insects, utilizing waxes and fats to a large extent, must secrete powerful lipases. If this supposition is correct, then bacteriolysis need not be related to proteolysis.

In order to obtain some information concerning the nature of bacteriolysis, we first made some investigations to determine the action of ferments such as trypsin and leucoprotease on bacteria. Kantorwicz, who has studied this subject most carefully confirms the older observations of the absence of digestion of the intact cells, whether living or dead, and showed that heating Gram-negative organisms to 70° C. made them lose their power of resistance, while Gram-positive organisms resist digestion even after boiling. He concluded that the resistance was due to an antiferment. He subsequently found that dried organisms were also resistant to digestion, but lose their resistance after being extracted with acetone.

Knowing that the unsaturated fatty acids are antitryptic, and that their inhibition is proportional to the degree of unsaturation, it seems reasonable to assume that bacteria might resist digestion in a degree proportional to the amount of unsaturation of the lipoids they contained. It will be remembered that Kantorowicz found that the antiferment was removed from the bacteria when they were ground up and extracted with acetone.

In experiments made with tubercle bacilli, we found that



their digestion by trypsin was in proportion to the amount of lipoids contained. Those organisms containing 31% of lipoids gave only 23% of digestion, while partially extracted bacilli which contained 7% gave 57% of digestion. These bacilli were old and had been killed by heating at high temperatures, and as a consequence some of the unsaturated fatty acids may have become oxidized. It is probable that recently grown organisms under these conditions would give still less digestion with trypsin. Similar results were obtained with other organisms, both Gram-negative and Gram-positive, and it was found in every instance that previous extraction with ether almost doubled the amount of digestion.

Digestion in per cent.

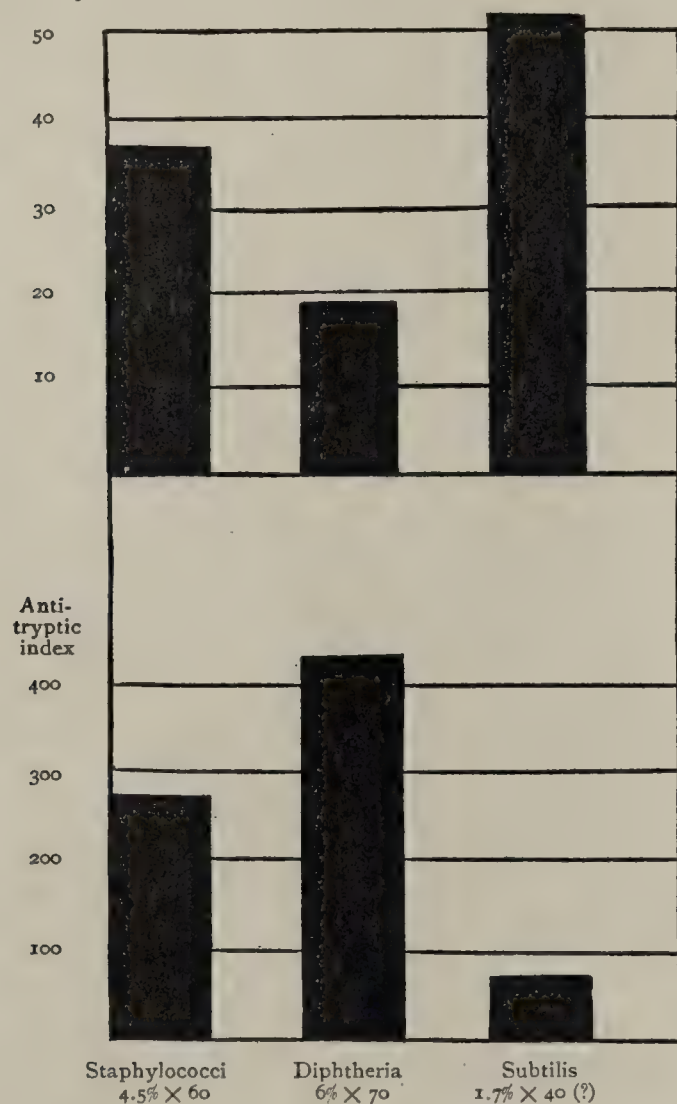


CHART 4.—Relation of the antiferment index to the rate of digestion of Gram-positive organisms.

The lipoids obtained by extracting various organisms with ether were saponified and tested for their antiferment properties, and in each case the ferment-inhibiting action of the soaps was found to be proportional to the degree of unsaturation.

We next studied the comparative rate of digestion of bacteria, in its relation to the contained lipoids. As a result of these experiments we found that we could determine the lipoidal antitryptic index by multiplying the percentage of lipoids by the iodine value. That is, those organisms containing a high percentage of lipoids with a high iodine value were always more resistant to the actions of ferments, and digestion was in inverse proportion to the figures obtained by multiply-

ing these two factors. Thus, unextracted tubercle bacilli gave the highest figure according to this method and showed the smallest amount of digestion. The diphtheria bacilli came next, while subtilis bacilli showed the lowest figure and the largest amount of digestion. These statements hold true for all the organisms tested.

That the bacterial lipoids influence the intracellular proteolytic activity of bacteria becomes apparent when we compare the amount of non-coagulable nitrogen contained in various organisms. Thus diphtheria bacilli, with a high antiferment index, have only 5% to 7% of the nitrogenous material in a non-coagulable form, whereas in subtilis bacilli, with a low antiferment index, a correspondingly greater protease activity is indicated by the presence of 33% to 35% of the total nitrogen in a non-coagulable form. Staphylococci, typhoid bacilli, and colon bacilli occupy an intermediate position. This influence is analogous to the effect of the antiferment on the protein metabolism of higher organisms, as we shall show later.

The antiferment is probably the agent concerned in preventing excessive protease action, or autolysis, in the cells. It is easy to understand that in dead bacteria the antiferment property may be greatly lessened by changes in the state of dispersion of the lipoids brought about by the increase in acidity. This lowering of the antiferment property of the unsaturated lipoids by a change in their dispersion is most easily demonstrated with serum antitrypsin. The morphological expression of the process is possibly to be found in the development of the so-called myelin figures present in cells during the early stages of autolysis. Possibly the increase in the rate of autolysis following the addition of certain inorganic colloids to the liver emulsions, noted by Ascoli and Izar,<sup>29</sup> depends on adsorption of the lipid antiferments.

It is probable that in Gram-positive organisms the lipoids are in more intimate association with the protein molecule, so that when dispersion changes are brought about, as by heating, the relative protection by these lipoids remains unaltered. This idea finds support in the fact that the lipoids from Gram-positive organisms resist extraction by lipid solvents to a greater extent than those from Gram-negative bacteria.

#### BACTERIOLYSIS:

The relation of proteolytic ferments of the serum to immunity reactions, particularly to bacteriolysis, has interested numerous investigators, and in view of the recent work of Abderhalden and his collaborators, it merits attention quite apart from a theoretical consideration.

The study of possible proteolytic cleavage during bacteriolysis, because of the manifest technical difficulties entailed by the accurate determination of nitrogen in the small amounts available, has been limited to rather general statements, based in most instances on experiments carried out with the Sorensen method. This method, being an index of the total cleavage of the protein molecule, gives no information as to the change from coagulable to non-coagulable forms, and is used in estimating peptolytic or ereptic enzyme activity rather than pro-



teolytic changes. For a like reason it represents the splitting of the protein bodies to non-toxic fragments in contradistinction to the splitting of the whole non-toxic protein molecule to the higher non-coagulable but toxic forms (proteoses).

The bactericidal and bacteriolytic property due to the action of complement and amboceptor has been assumed, more particularly by French and German writers, to be enzymotic in character, and in the nature of a protease action. There is, however, no experimental basis for this idea; indeed the fact that complement action is not identical with protease action can be demonstrated in a very simple experiment. When chloroform is added to fresh serum and thoroughly mixed, the complement is rapidly destroyed; the serum protease, however, first becomes active under these conditions, as was first shown by Delezenne and Pozerski.<sup>30</sup> The activation of the ferment under the influence of chloroform or other lipid solvents is due to the fact that the antiferment is removed. There should, therefore, be no confusion as to the non-identity of these serum constituents.

If complement activity is enzymotic in character, we should rather seek to identify it with the lipase or allied enzymes. The substrate offered for complement action—red blood cells, animal cells, bacteria—is lipoidal in nature, the potentially lipoidal character of the limiting membranes of the corpuscles and animal cells being well established and rendered more than probable for bacterial cells. The fact that powerful proteolytic enzymes are without effect on such substrata is almost conclusive evidence that the surface of these substrata are not protein in nature. The observations of Metchnikoff, to which we have already referred, are of special significance when we discuss the phenomenon of bacteriolysis.

The experiments,<sup>31</sup> designed to determine the amount of proteolysis occurring during bacteriolysis, were carried out with emulsions of washed bacteria. The bacteria after treatment with serum were centrifuged and washed, and the total nitrogen and non-coagulable nitrogen was determined in the sediment and in the supernatant fluid.

Briefly, the results of the experiments show that the greatest loss of bacterial nitrogen was in the mixtures containing immune serum and complement, indicating a marked lysis of the bacteria. There is, however, no corresponding increase in non-coagulable nitrogen obtained in the supernatant fluid. In other words, there is no relation between the amount of lysis and proteolysis.

In view of the established fact that the serum of practically all animals contains an active antiferment against trypsin, leucoprotease, and the autolytic ferments, we can hardly expect a result other than that noted in the above experiments; *i. e.*, that bacteriolysis is not associated with proteolysis.

One of us with Strouse has called attention to the fact that mere solution of bacteria should not be confused with proteolysis; the former might be due to purely physical factors, as when organisms are kept under lipoidal solvents as preservatives. This distinction should be made with equal emphasis for the immunity reactions.

If bacteriolysis is not associated with proteolysis we must

find some other explanation. This, we believe, should be sought in the relation of the lipoids of the bacteria and the lipolytic effect of the serum. That a physical change of some sort is induced in corpuscles treated with immune serum and complement has been shown by Eisner and Friedemann,<sup>32</sup> and is indicated by the fact that bacterial organisms are rendered more digestible for trypsin.

#### ABDERHALDEN REACTION.

Our results might be considered to contradict those obtained by several workers with the Abderhalden dialysis method, who have observed an increase in protein split products when bacteria were allowed to digest with immune serum (Voelkel).<sup>33</sup> These workers have ignored the presence of an excess of antiferment in the blood, assuming that proteolysis might take place under normal conditions with the resultant splitting of bacteria.

Numerous experiments made during the past year have convinced us that the same explanation applies to the Abderhalden reaction. Normal human serum rarely contains strong proteolytic ferments, and therefore does not give a positive Abderhalden reaction. On the other hand, sera of pregnant women, of patients with pneumonia, or with cachexia due to certain causes, do contain ferments and will give positive Abderhalden reactions.<sup>34</sup> We were able to obtain positive Abderhalden reactions with all human sera containing strong proteolytic ferments, regardless of the disease from which the patient was suffering, not only with placental tissue, but also by extracting the antitrypsin with chloroform, or adsorbing it with starch. In addition we found that those agents which adsorb antitrypsin most readily, are the ones which give the strongest Abderhalden reactions.

We must conclude from our results that proteolytic ferments capable of attacking only specific proteins, such as bacterial or placental proteins, do not exist. Proteolytic ferments are present in the blood under certain conditions, but they are not specific, and become evident only when the antitrypsin has been removed. A positive reaction is due to the adsorption of the antitrypsin by the placental tissue, or by the bacteria, and this permits the ferment to act on the exposed serum protein.

#### PROTEIN METABOLISM.

During the progress of this work we were impressed more than once with the possibility of a relation existing between the antiferment of the blood and the protein metabolism. Rosenthal<sup>35</sup> has demonstrated a decrease in the antiferment power of the blood of animals during starvation; the converse, an increase in the antiferment after feeding, had been noted by Zunz<sup>36</sup> and others. In view of the fact that Schulz,<sup>37</sup> and Heilner and Poensgen<sup>38</sup> have recently shown that during starvation a proteolytic ferment can be demonstrated in the blood in the period just preceding and during the high pre-mortal excretion of nitrogen, we considered it of interest to ascertain in greater detail the alterations in the relative balance between ferment and antiferment in the serum of animals



during inanition.<sup>39</sup> Both Schulz, and Heilner and Poensgen assume that the enzyme activity, which they have demonstrated, is due to the presence of a new ferment in the blood. The observation may, however, be interpreted as being simply due to a reduction of the anti ferment with a resulting freeing of protease action.

Free protease action in the blood is not compatible with continued life because of the intoxication of the organism by the higher cleavage products of the proteins formed during hydrolysis. If during starvation such a state actually obtains, might it not be possible to explain the premortal rise in nitrogen excretion and the death of the animal itself on the basis of an autointoxication with protein split products?

Probably the most striking feature of the metabolic process during starvation is the so-called premortal rise in nitrogen excretion. Were this phenomenon due to a gradual attack on body proteins we might expect a correspondingly slow rise in nitrogen excretion. This, however, seldom occurs; the increase is sudden, almost explosive in character, and the excretion remains high until death occurs. Schulz has possi-

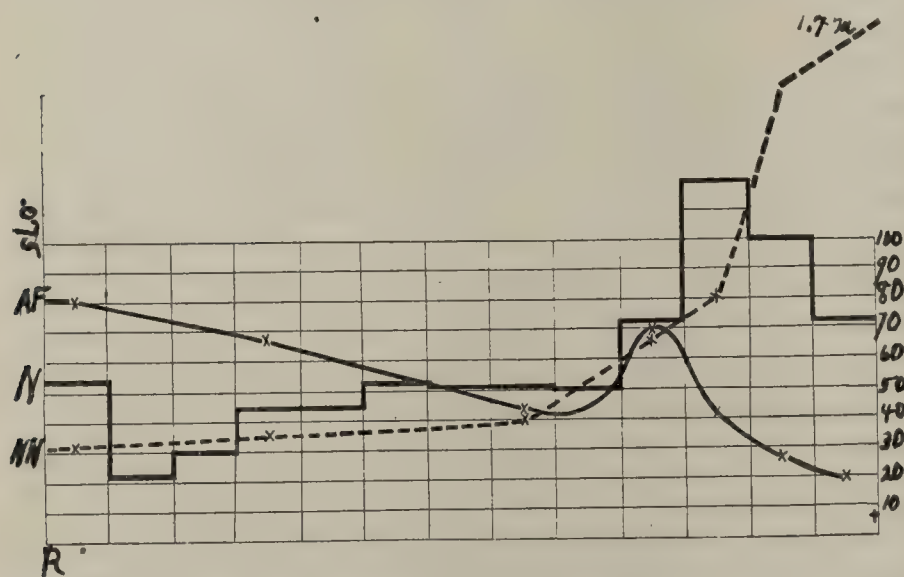


CHART 5.—AF, antitrypsin; N, urinary nitrogen; NN, non-coagulable nitrogen in 1 cc. of blood.

bly interpreted the picture most clearly. He assumes that during starvation we are dealing with either a low grade chronic intoxication, or a series of more acute shocks arising from toxic substances produced in the organism; the manifestations being occasional periods of fever, malaise and weakness. Schulz concludes that the final rise in nitrogen excretion is due to such an intoxication with resulting tissue destruction.

Our experiments were conducted with dogs and rabbits. The animals were kept in metabolism cages with constant access to water but without food. Care was taken to avoid unnecessary handling and to keep the temperature of the room constant. The small amount of blood needed was taken from the ear vein. Chart 5 shows graphically the results obtained with a rabbit.

In the first experiment the results of the alteration of the anti ferment balance are readily seen. The gradual rise in the non-coagulable nitrogen is coincident with the gradual reduction of the anti ferment, a reduction which continued until the 20th of July, when evidently the enzymotic power overbalanced the inhibitory, and the non-coagulable nitrogen began

to rise rapidly. It is at this time that the intoxication begins, and during this period, too, it will be recalled, Schulz, and Heilner and Poensgen have shown the proteolytic activity of the serum. This protein intoxication is followed by a rise in antitrypsin, as is the case following anaphylaxis, anaphylatoxin, and serotoxin injections, or after burns; the injury to the cells resulting possibly in a liberation of unsaturated lipoids from the cells which then enter the circulation in a state of colloidal solution. These lipoids are, however, metabolized rapidly, the antitryptic titre falls while the non-coagulable nitrogen, representing the ferment action of the proteases, continues to rise at a rapid rate. The premortal rise in nitrogen excretion probably represents then a protein intoxication, an intoxication due to the lowering of the balance between the ferment and the anti ferment, the consequent activation of ferments normally present, and the resulting formation of toxic split products from proteins. The short rise in antitrypsin following this intoxication is probably another manifestation of the same process. These experiments were repeated several times with dogs and rabbits and similar results obtained in each instance.

Apart from any clinical bearing, these experiments offer several confirmatory lines of evidence in regard to the nature of serum antitrypsin and its relation to the protein metabolism of the organism.

That the rate of protein metabolism is intimately influenced by the amount of anti ferment in the blood is indicated by the following table, in which the average antitryptic index for the first five days of starvation of four rabbits is compared with the total amount of urinary nitrogen excreted:

Animal No.	Per Cent Inhibition	Nitrogen Excreted
1	41	4.24 gm.
2	66	2.95 "
3	71	1.97 "
4	73	1.99 "

The excretion of nitrogen seems to be inversely proportional to the anti ferment index.

We can therefore understand that such substances as the iodides, which lower the anti ferment, should be associated with an increase in protein metabolism, while egg fats and unsaturated oils—olive oil, cod-liver oil—will tend to increase the anti ferment index and in this way depress protein metabolism, and so indirectly lead to a storage of nitrogen apart from any intrinsic food value in themselves.

The results of the experiments which we have just described tend to shed considerable light on the action of the iodides in causing absorption of necrotic material. Iodin has been used for years, yet little is known concerning its action in the body. This lack of knowledge applies particularly to its activity in causing the absorption of necrotic material such as is found in gummata.

The results obtained with iodides have been variously ascribed to their influence on the general metabolism of the body; to their supposed action in causing a lowering in blood pressure; to changes in the viscosity of the blood; to lympho-



cytosis; to an increase in the activity of the lymphatics and, to the oxidizing properties of nascent iodine.

Time will not permit us to discuss the work done by Binz,<sup>40</sup> Hinz,<sup>41</sup> Romberg,<sup>42</sup> Müller and Quada,<sup>43</sup> Determan,<sup>44</sup> Stockman and Charteris,<sup>45</sup> Lehndorff,<sup>46</sup> Macht,<sup>47</sup> and others, in regard to the pharmacologic action of iodine. McLean<sup>48</sup> made a study of the distribution of iodine in the bodies of rabbits which had received several doses of potassium iodide, and found that the lipid fraction contained 32% and the water soluble fraction 67%, while the extracted protein contained no iodine. This work would seem to disprove the older view that iodine combines with the proteins of the body.

We confined our investigations to the action of iodine on the antitrypsin of the blood, as we believed that antitrypsin is the most important agent in preventing the absorption of necrotic material such as is found in infarcts and in caseous areas in syphilis and tuberculosis. The knowledge that the antiferments of the blood and of tuberculous caseous matter are

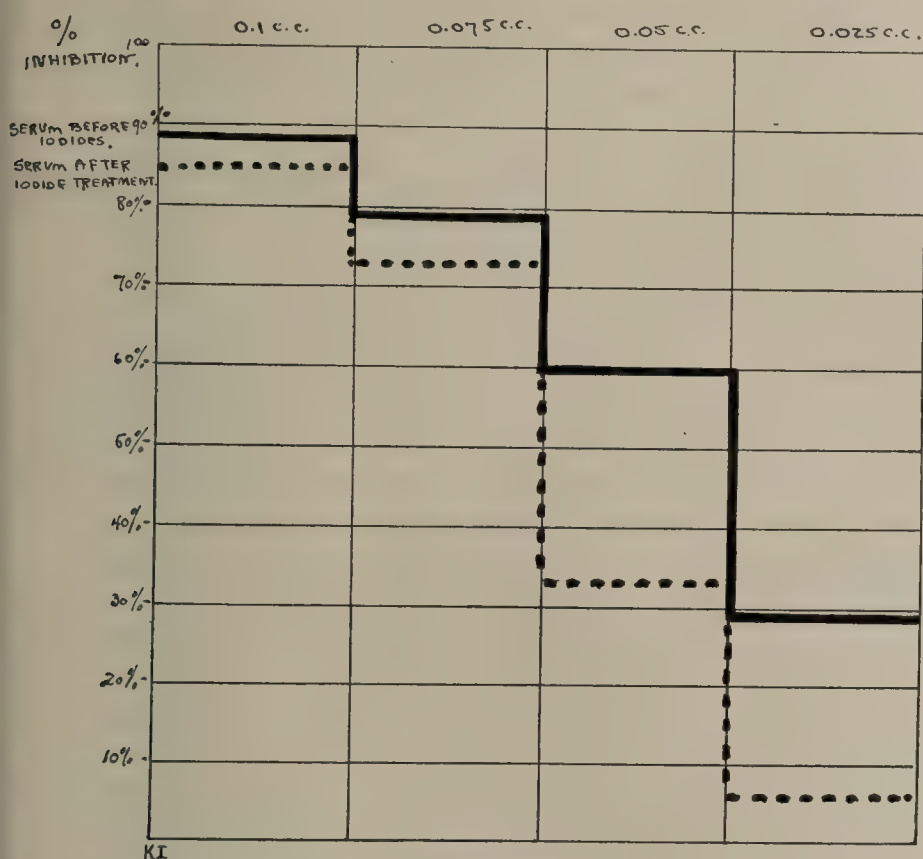


CHART 6.

unsaturated fatty acids, suggested to us the possibility that the action of iodine in the body may be due to its combination with these fatty acids, thus causing a neutralization of their activity as ferment-inhibiting agents. If this supposition is true, the neutralization of the activity of these agents should lower the anti-enzyme strength of tissues in general and permit the removal of dead tissue by autolysis.

We are indebted to Drs. Fordyce, McMurtey and Sharpe, of the Vanderbilt Clinic, New York City, for furnishing us with the clinical material used in this study. Thirteen patients were studied, 11 of whom were syphilitics. In each instance the blood was tested before iodides were given, and then at frequent intervals until the patient reached the limit of tolerance.

This series of cases is not large, but is sufficiently so to show that iodides administered to human beings cause a very con-

siderable reduction in the antitryptic activity of the blood. The difference is not so evident when larger amounts of serum are used, as here there is an excess of the enzyme-inhibiting agent over that necessary to neutralize the amount of trypsin used; but in greater dilutions the difference is very obvious.

It is interesting to note that in the two patients of the series who developed iodism, the antiferment was very much higher than it had been during the course of treatment. This increase in antitrypsin may be due either to the failure of the iodine to combine with the unsaturated fatty acids, or to the mobilization of lipoids as the result of the toxic action of the iodine. Large doses of iodides may cause the neutralization of the antiferments in localized areas, or in the cell wall with the consequent destruction of cells by the ferments present and the liberation of lipoids. This may partially explain the toxic action of iodine.

#### SYPHILIS.

In order to arrive at some understanding concerning the action of iodine in syphilis two points must be considered: (1) Does it destroy the infecting organism? (2) Does it merely bring about resolution of the process and leave the infecting organism to produce similar lesions?

Authorities on this subject are unanimous in the belief that iodides are not curative in the sense that they prevent the return of the lesions, this can be accomplished only when the iodides are combined with some other form of treatment. Tomaszewski<sup>49</sup> found that the administration of iodine does not prevent the development of experimental syphilis in monkeys and rabbits, neither has it a curative action; but iodized animals recovered quickly when given mercury.

As experimental work and clinical observations have demonstrated that iodides do not destroy the infecting organism, we must assume that the results obtained are due to the power the iodides possess of causing resolution of the lesions. That this actually occurs will be attested to by every clinician of experience.

Owing to its scarcity we have not been able to examine material from gummata, and so we are unable to state positively that the antienzymes present are similar to those found in tuberculous caseous material, but it is probable that the same agents are active here also as in anemic infarcts in which autolysis does not occur. If this assumption is correct, it is not difficult to explain why large gummata rapidly disappear when the patient is brought under the influence of iodides. It is due to the fact that unsaturated fatty acid radicals which inhibit autolysis, have become saturated with iodine. As soon as this occurs, the ferments which are present, or which may be brought in, become active, autolysis takes place, and the necrotic tissue is absorbed. Here, also, the local action of the ferments is made less difficult by the reduction of the antienzyme in the circulating blood. It must be borne in mind that the iodides are not as effective in the earlier stages of syphilis when necrosis of tissue is not so evident.

If the above interpretation of the action of iodine is correct it gives the clinician a rational idea of what he is accomplishing



when he gives iodides to a patient in the tertiary stage of syphilis. According to this view, iodine neutralizes the action of the agents which prevent resolution and absorption of the diseased or necrotic tissue, and at the same time lays bare to the action of the real germicidal agent the infecting organism which previously had been protected by necrotic tissue. With the exposure of the infecting organism, such agents as mercury and salvarsan would be much more effective.

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## DISCUSSION.

DR. HOWELL: I do not feel well qualified to discuss Dr. Jobling's paper in a critical way, but I should like to express the great interest I have felt in it and to ask some questions. The fundamental facts presented by Dr. Jobling are in themselves interesting and suggestive, and of course the very wide application to nutritive conditions adds greatly to our feeling that we are dealing here with phenomena that may be very significant. As a student of the blood, my attention was attracted particularly by Dr. Jobling's statement that his sera freed from lipid by chloroform show a strong tendency to produce intravascular clotting. As thin sera are cytotoxic, it is possible that they may have an immediate destructive effect on the blood-platelets and thus bring about intravascular coagulation. I should like to ask whether platelet counts were made after the injection of the washed serum. The protection conferred upon the living cell by the presence of lipoids with a high iodine value, as emphasized by Dr. Jobling, suggests naturally to the physiologist that herein may lie the explanation of the protection of the intestine from self-digestion by trypsin. The experiments seem to put this antiferment theory on a more probable and comprehensible basis. In regard to the application made of the facts to the explanation of the Abderhalden reactions, it is of course difficult to judge. Most physiologists have accepted the fundamental assumption underlying these reactions, namely, that the tissues can form protective enzymes. I should like to remind Dr. Jobling that this assumption seems to hold in the case of foreign carbohydrates injected into the blood as well as in the case of foreign proteins. Can the change in the antitryptic lipid be used to explain both cases? The application made of his facts by Dr. Jobling to explain the ante-lethal rise in nitrogen excretion in the cases of prolonged starvation is quite novel to me. Physiologists had accounted for this phenomenon in an apparently satisfactory way by the assumption that it marked the period when the body-fat had been consumed and the animal was thrown upon his protein tissues alone. Both facts might of course be correct—the fall in antitrypsin might coincide or be connected with the consumption of body-fat, or it may be that they are entirely independent. I should like to ask Dr. Jobling whether experiments have been made that rule out the older explanation. Dr. Jobling's ideas are certainly stimulating. The possibilities that suggest themselves on the basis of this balance between the proteolytic and protective enzymes to the body are many and I have no doubt that they will call out a great deal of investigation.



DR. JOBLING: I am glad that Dr. Howell brought up the subject of specific ferments for foreign carbohydrates. In using the terms ferment and antiferment I was referring only to proteases and antiproteases. We have not done any work with the carbohydrates. We cannot accept Abderhalden's statements of having demonstrated the presence of specific immune ferments for carbohydrates. All the work done in immunity shows that immune substances are not present in the circulating blood for several days after an animal has been inoculated with the foreign substance. Abderhalden, however, found that the sera became active a few hours after the animals were inoculated. We believe that his work indicates that these ferments are normally present in the body, but are mobilized only when the foreign carbohydrates are introduced into the general circulation.

Dr. Howell's suggestion that the intravascular clotting may be due to the destruction of platelets by the extracted sera is very interesting and may prove to be the explanation. Platelet counts were not made. Von Behring has recently advanced the view that the intoxication in anaphylaxis is due to thrombi composed of coagulated platelets.

Our inanition experiments were conducted to determine the relation of the serum ferments and antiferments to the nitrogen excretion. We had already shown that sera containing proteases become toxic if the antiferments were removed and it seemed reasonable to assume that the same thing occurred in the body, as the maximum nitrogen output in the animals corresponded in time with the minimum amount of antiferment. We were under the impression that Lusk and others had shown that an animal may die of starvation while the body still shows considerable fat.

## NOTE ON THE ANTAGONISM BETWEEN THE LACTIC-ACID AND THE SPORE-BEARING ORGANISMS IN MILK.

By WILLIAM S. KESTER, M. D.

(From the Laboratory of Hygiene and Bacteriology of The Johns Hopkins University.)

It has now been shown by a number of observers that the predominant organism in milk is the lactic acid bacterium known usually as *Streptococcus lacticus* for which, however, the name *Bacterium guntherii*, Lehmann and Neumann, is probably the correct designation.<sup>1</sup> Under normal circumstances these organisms multiply and crowd out the aerobic and anaerobic spore-bearing bacteria. If the lactic acid organisms are destroyed by heating the milk to a temperature of 70° C., however, the spore-bearing organisms multiply rapidly.<sup>2</sup> It becomes a matter of interest, therefore, to study more carefully the series of changes occurring in the aerobic bacteria in milk heated to various temperatures below 70° C. To determine these changes samples of market milk were heated to temperatures ranging from 55° C. to 70° C. for 30 minutes and cultures made at various intervals. The results obtained from the examination of a considerable number of samples may be summarized as follows:

Plates poured from raw milk reveal usually a mixture of lactic acid bacteria, pigmented air organisms, and intestinal species which may be placed in the coli-aërogenes group. Only rarely did colonies of spore-bearing bacteria appear on the plates. If this milk be incubated at 37° C., it clots firmly and cultures show a multiplication of the lactic acid organisms and the coli-aërogenes forms to the general exclusion of the pigmented and spore-bearing species. By the end of from 48 to 72 hours the lactic acid organisms are usually predominant but the intestinal forms may also persist. Milk heated to 55° C. for half an hour shows on plates poured immediately a mixture of lactic acid organisms, intestinal forms and sporulators. The last form an appreciable feature and in this respect the plates differ essentially from the raw milk plates in which the sporulators are rare. When this milk is incubated it also clots in the manner of raw milk and plates poured at the end of 24 hours reveal no spore-bearing bacteria. These species have evidently been overgrown by the lactic acid organ-

isms and the representatives of the coli-aërogenes group. Milk heated to 57.5° C. reveals practically the same phenomenon. At 60° C., however, a distinct change in the sequence of events is evident. On plates made immediately after heating, the spore-bearing bacteria are almost as abundant as the non-spore-formers. At the end of 24 hours the milk is usually firmly clotted and cultures show the two groups of organisms in about the same relative abundance. Soon peptonization sets in and eventually the clot in the milk completely disappears. Cultures after 48 to 72 hours reveal an increase of the lactic acid bacteria and the intestinal forms with a coincident disappearance of the sporulators. This change in the clot is probably to be ascribed to the peptonizing action of the spore-bearing aerobic and anaerobic bacteria, many of which secrete energetic peptonizing ferments. The disappearance of the sporulators may be due primarily to the rapid multiplication of the lactic acid organisms. It must also be remembered that *Bacterium welchii* (*B. aërogenes capsulatus*) is always present in milk and multiplies in milk heated to 60° C. It may also take part in the destruction of the sporulators, since, from the work of Shippen,<sup>3</sup> we know that such an action is possible. Whatever be the causation of the phenomenon, milk heated to 60° C. reveals a clotting usually followed by complete peptonization with a coincident multiplication of lactic acid organisms, so that by the end of 48 to 72 hours the aerobic plates show only these forms. This reaction is not universal, however, and at times the firm clot which is seen at the end of 24 hours, remains unaffected, probably as the result of the survival of sufficient numbers of lactic acid organisms to prevent the multiplication of both the aerobic and anaerobic spore-bearers.

In milk heated to 63° C. and to 65° C. the same phenomenon is seen. The milk first clots and then rapidly peptonizes, while cultures show the sporulators gradually yielding to the intestinal and lactic acid bacteria. At 67° C. the last two groups



are usually completely destroyed and in milk heated to this temperature the spore-bearers multiply rapidly. After peptonization has been completed, however, the aerobic cultures are frequently sterile and in such instances the destruction of the sporulators is best ascribed to the multiplication of *B. aërogenes capsulatus*.

From the various observations the following conclusion may be drawn.

#### CONCLUSION.

The heating of market milk to temperatures ranging from 55° C. to 65° C. for 30 minutes results in a destruction of many of the lactic acid and intestinal bacteria, and in such samples sporulating bacteria can always be found on the plates poured within 24 hours. After this time the lactic acid and the intestinal bacteria become the predominant species in the

milk. The disappearance of the spore-bearers is to be attributed to the growth of the lactic acid organisms in some instances, to *Bacterium welchii* in others, and possibly is due to their combined action. At 67° C. the lactic acid and intestinal bacteria are usually completely destroyed and in milk heated to this temperature the spore-bearing organisms multiply rapidly from the start, but may at times yield to the "gas bacillus" in which case aerobic cultures may be sterile.

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# BULLETIN

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## STUDIES ON THE CEREBRO-SPINAL FLUID AND ITS PATHWAY, NO. IX.\*

### CALCAREOUS AND OSSEOUS DEPOSITS IN THE ARACHNOIDEA.

By HARVEY CUSHING and LEWIS H. WEED.

(From the Laboratory of Surgical Research, Harvard Medical School.)

*Introductory.*—In the course of certain investigations undertaken in the laboratory dealing with the cerebro-spinal fluid, special attention has been paid to the determination of the pathway by which the fluid escapes from the subarachnoid spaces into the dural sinuses. It was histologically demonstrated by one of us (Weed, in No. III of the Series,) using a method of injection with subsequent precipitation of granules, that the arachnoid villi or tufts, which though widely distributed project into the dura in greatest number along the course of the larger venous sinuses, represent the chief points of exit for the fluid.

The animals employed for the experiments were chiefly cats, dogs and monkeys, and though macroscopically the meninges appeared normal in every respect, in a small percentage of the specimens the arachnoid showed microscopical evidence of a pathological change, in the shape of small bodies found embedded in the membrane which gave the characteristic tinctorial reactions for calcium. Interest in these bodies was further

accentuated by the finding of wholly similar structures in the human leptomeninx where it was possible to trace, often in a single individual, the various stages of their development. We wish to redirect the attention of pathologists to the occurrence of these calcareous depositions and to emphasize their relation to the mesothelial clusters of arachnoid cells incorporated in the dura.

*Historical.*—Degenerative processes have occupied the attention of pathologists since the establishment of the cellular doctrine and there is an extensive literature on the subject of calcareous degenerations in particular, though the hypotheses regarding this particular form have become modified since the introduction of new viewpoints, particularly of a physical-chemical nature, into cell-chemistry. From Virchow's<sup>22</sup> original dictum that calcification follows upon a local or general disturbance of the nutritive processes of the tissue, some have come to view such a deposition as an evidence of a change in the colloidal reaction of the cell-structures (Lichtwitz<sup>14</sup>). In the interval which elapsed between two conceptions, many observers (Grohe,<sup>10</sup> Hirschberg,<sup>11</sup> Czeck<sup>6</sup> and others) were concerned with the problems of the so-called "Kalkmetastasen" in the sense of Virchow. Still others (notably Gierke,<sup>9</sup> Schmorl,<sup>21</sup> and Hueck,<sup>23</sup>) became interested in the possible

\* The previous articles in this series have been published as follows: Numbers I to VII inclusive, *Journal of Medical Research*, 1914, XXXI, pp. 1-176; Number VIII, *American Journal of Physiology*, 1915, XXXVI, pp. 77-103.



presence of iron salts in the various calcium depositions in the pathological tissues of the body. And yet another group has attacked the problems of calcification and ossification from the chemical or experimental side (Wells,<sup>24</sup> Moore, Joseph and Williams<sup>17</sup>).

Particular attention has been paid to the occurrence of deposits of lime salts within the cerebro-spinal axis since Virchow called attention to the presence of small calcified bodies in that type of cerebral neoplasm which he designated "Psammoma." Not only have these peculiar structures (the so-called psammoma bodies, brain sand, corpora amylacea) been found in the one type of tumor described by Virchow, but they have also been described in practically all classes of slowly developing cerebral neoplasms. In a study of a series of brain tumors, made in Mott's laboratory, depositions of calcium salts were found by one of us<sup>23</sup> in 40% of all cases.

But apart from the occurrence of such degenerative processes in the cerebral new growths, the deposition of calcium salts appears to be a normal physiological phenomenon in two adult human structures within the central nervous system, the corpus pineale and the plexus choroideus. Meyer<sup>16</sup> has differentiated morphologically the calcified bodies in these two situations and has shown that the neoplasms arising from them contain the typical form of calcareous bodies found in the gland of origin. In a discussion of calcification and its occurrence in various tissues other than in the pineal gland and choroid plexus, von Recklinghausen<sup>20</sup> called attention to the localized calcareous granules in the meninges, but gave no detailed account of the process. True bony growths in the shape of osteophytes arising from the meninges are of frequent occurrence and osseous deposits in the arachnoid in the form of plaques have been repeatedly recorded, for the most part, as unimportant descriptions of individual cases (Brinton,<sup>3</sup> Burton,<sup>4</sup> Evans,<sup>7</sup> Potts,<sup>19</sup> Fletcher<sup>8</sup>). But if one agree with Paulicki,<sup>18</sup> who long ago differentiated calcification from ossification on the basis that the former represents a degenerative process, while the latter is solely hyperplastic as evidenced by the vascularization and proliferation of osteoblasts, the reports in the literature concerned with meningeal calcification as a separate process have been few.

Probably the two most important communications dealing with calcification in the arachnoid are those of Zanda<sup>25</sup> and of Levi.<sup>13</sup> The former made studies of the osteomata arising from the spinal arachnoid with especial reference to their stages in development and to the subsequent vascularization. On the inner surface of this leptomeninx near the site of the outspoken osseous tumor, he observed distinct nodules which varied in size from those barely visible to the unaided eye to masses several millimeters in diameter. Microscopically, they were composed of concentric layers of cells in the midst of similar circular strands of connective tissue, while in the center of each mass was found a calcified body, usually exhibiting characteristic concentric rings. From this elementary stage, Zanda traced the subsequent osteoma through a formation of sclerotic rings of connective tissue about the primary calcareous body to a final vascular invasion of the increasing calcified area by

vessels coming from the dura. Of interest in our problem is Zanda's division of the primary calcified bodies into those which arise from the connective-tissue fibers and those which apparently come from cells.

Levi,<sup>13</sup> in an excellent inaugural dissertation, dealt with the occurrence and the significance of calcified concretions in psammoma tumors as well as in the plaques which occur in the spinal arachnoid. In the cerebral neoplasms, he observed a cellular reaction or hyperplasia about the calcified body, and suggested that the calcium salts were for the most part laid down in degenerated cells. In the plaques found in the spinal arachnoid, the cases apparently fell into the two classes proposed by Zanda; in one, the calcium deposition occurred in the midst of an endothelial cell hyperplasia, while in the other the lime salts were found in the connective-tissue strands composing the trabeculae of the arachnoidea.

*Personal Observations on Calcified Bodies in the Arachnoid.*—Our attention was first directed, in 1912, to microscopic abnormalities in the arachnoid membrane in healthy animals by the observation of a peculiar proliferation of the arachnoid mesothelium in the meninges of a cat. The animal was a young adult, whose brain and cerebral meninges had been sectioned for study of the meningeal relations in the region of the superior longitudinal sinus. Similar hyperplasias of the arachnoidal mesothelium were occasionally encountered in the course of our studies of the next two years, during which period many specimens of the arachnoid, both of man and also of the lower animals, were serially sectioned. Though our chief concern lay with the structure and function of the normal arachnoidal villi which penetrate the dura, our interest was naturally extended to this proliferative process occurring in the cells composing these structures. Though the proportion of laboratory specimens in which we observed examples of cellular hyperplasia was small, the process was almost invariably associated with the deposition of lime salts in the membrane, and many of the stages in the formation of the calcareous masses have been observed.

The general process of calcification in the arachnoid must necessarily differ somewhat from that in other portions of the organism, for in this structure we are dealing with a membrane, whose nutritive exchanges are derived from the circumambient cerebro-spinal fluid rather than from the circulating blood. Again the process is modified somewhat by the fact that the connective-tissue elements of the arachnoid are slight in amount and quite insignificant as compared to the mesothelial cell clusters which surmount the arachnoid villi.

The initial step in the formation of calcium depositions in the arachnoid appears to be a proliferation of the mesothelial cells of the membrane. Such a hyperplasia is usually best seen in the neighborhood of the arachnoidal tufts or villi which, as is known, project into the dura, particularly in the region of the great sinuses.

Stages of the degenerative process commonly observed in these cell clusters are illustrated in the first six figures. In Fig. 1 is shown a clumping of the nuclei in a small cell cluster on the outer surface of the arachnoid membrane of a cat. In



this clump of nuclei, the typical chromatin masses and strands which characterize a normal nucleus, have been lost and, although the external nuclear form is retained, a homogeneous mass appears. The process is associated with an infiltration of calcium salts, definitely limited to the small clump of arachnoid cells, the test of calcification in this as in all cases being the characteristic staining reaction with hematoxylin confirmed by silver nitrate reductions. The nuclear forms stand out distinctly from the remainder of the infiltrated area, suggesting that there is either a primary deposition of calcium in the nuclei or that they possess a greater affinity for the circulating calcium in solution. The arachnoid cells and stroma of the surrounding membrane appear normal in every respect.

An intradural invagination of hyperplastic arachnoidal mesothelium of larger size, which has undergone much the same degenerative change, is shown in Fig. 2 taken from the meninges of a dog, the nuclei of the cells having lost their intranuclear structure with subsequent deposition of calcium elements. The sparse internuclear substance has also been infiltrated, though to a lesser degree, with similar salts, the nuclear outlines being still apparent even though both nuclei and scanty cytoplasm have become calcified. No calcium deposits can be made out in the true dural tissues except in relation to the arachnoid cell-column. Along the periphery of the degenerated cells may be seen other nuclei of leptomeningeal origin which appear to be normal in character.

In Fig. 3 there is shown a small area of arachnoid tissue within the dura, which contains, arranged in the form of a circlet, a small number of calcified bodies, resembling in their external form and size typical arachnoid nuclei, but showing no intranuclear morphology. The degenerative process seems to be limited, as far as the infiltration with lime salts is concerned, solely to these minute nuclear-like masses. The intercellular substance and the cytoplasm are wholly unaffected by the calcium depositions. The rosette of calcareous bodies surrounds a small area which has apparently undergone slight homogeneous degeneration but without any invasion by lime salts. About this peculiar degenerated area are normal strands of dural fibers.

An interesting finding in the canine meninges, shown in Fig. 4, suggests a primary deposition of lime salts in other elements than the nuclei, which therefore need not be the sole factors in this process. In the midst of the arachnoid membrane occurs a small collection of normal arachnoid nuclei surrounding an area in which calcium salts have been deposited in tiny round and oval forms. These bodies are much smaller than the nuclei and between them there is a suggestion of a diffuse calcium infiltration.

Thus far we have been concerned solely with minute depositions of calcium salts and not with outspoken psammoma bodies or large plaques. In the series of the leptomeninges of man and of the lower animals, much larger calcareous areas have been found. Thus in Fig. 5 (from a cat) and Fig. 6 (from a monkey) there appear circumscribed calcified formations, which are limited to the arachnoid areas whether merely in apposition with the dura or incorporated within it. In some of

the bodies the tinctorial reactions for calcium are not marked; in others the infiltration is dense and sharply delimited. The number of the cells enveloping these calcareous centers varies greatly in the specimens as also does the more or less marked tendency to whorl formation on the part of the cells; but in all cases the association of the calcified deposits with arachnoid mesothelium is unmistakable.

This may be more clearly brought out by the section in Fig. 7, taken from the meninges of a man. Here is shown an arachnoid villus which projects through the dura into the sagittal sinus. The brain from which the specimen was taken had been under a long-standing pressure and consequently the villus appears distended and the outer layer of the arachnoid considerably thickened. Stages of the process to which we would call attention appear in the higher magnification of the blocked areas at A, B, C, and D. In Fig. 7A is a cluster of arachnoid cells which have undergone hyperplasia and which show the characteristic whorl formation commonly seen in the so-called dural endotheliomas. There is no tinctorial evidence of calcium deposition. Such a deposition does appear, however, in Fig. 7B, where in addition to whorl formation there is a sharply cut sand body. In Fig. 7C is another cluster of hyperplastic mesothelial cells lying at the neck of the arachnoid villus where it penetrates the dura, its appearance resembling closely the group of cells in Fig. 2, although no calcium deposition has occurred. Another sand body in process of formation with ghosts of nuclei still discernible appears in Fig. 7D, where it lies in a cluster of cells on the margin of the free arachnoid lining the subdural space.

The internal structure of the calcium body is always of interest, for in the more minute forms no obvious key to the method of deposition can be made out, whereas, in the larger depositions, each successive calcareous increment seems to have been recorded. The bodies thus formed may be lamellated and exhibit concentric rings resembling starch granules; or when the deposition is more irregular, amorphous concretions arise. The terms *corpora amylacea* (starch bodies) and *corpora arenacea* (sand bodies) are still often used interchangeably and were originally regarded even by Virchow as similar structures, until he demonstrated that they were distinguishable by the iodine reaction.

One of the most perplexing of the questions related to these depositions of calcium concerns the cellular increase which may be observed in practically all cases. Levi<sup>13</sup> and Zanda<sup>25</sup> have both described this phenomenon, but have not discussed its significance. Is this cell-proliferation the essential basis for the calcification or is it merely a reactive phenomenon as that against some foreign substance? Certainly in the fully developed cases of calcareous deposition, the cell reaction might appear to be wholly secondary to an original degenerative change. But this explanation for the cell-proliferation will not hold, as a general rule, when one examines the stages in the formation of such calcified bodies. The proliferation of arachnoidal mesothelium with a tendency to form whorls is not uncommon, and areas of the hyperplastic cells, associated in no way with degenerative changes, are often found in the dura.



Thus, in Fig. 7-A, can be seen an arachnoid cell-mass with the nuclei and internuclear material concentrically arranged, analogous in every respect to the cellular proliferation seen in Fig. 6, which surrounds a calcified body.

If one were to assume the cellular proliferation to be a reaction secondary to the calcium deposition, it should occur with some regularity, but in many of the specimens, there is but little tendency for a cellular hyperplasia to occur about the area of calcification. On the whole the evidence indicates that the cellular proliferation is not a phenomenon expressing reaction to the foreign body.

What, then, are the basic elements in which such calcareous depositions occur in the tissues within the dura? Many points of origin for psammoma bodies and for brain sand have been suggested in the past. Von Recklinghausen<sup>20</sup> believed that these minute calcareous bodies arose from sclerotic connective tissue in the various tumor forms within the nervous system. He premised that an increase in the cells on the periphery followed the deposition of lime salts in the center. Bizzozero<sup>2</sup> described hyaline bodies, possibly of nuclear origin, which may be the substance in which the lime salts are deposited. Quite in accord with these observations are the two divisions of the bodies made by Zanda<sup>25</sup> and corroborated by Levi.<sup>13</sup> The calcareous masses in the arachnoid may, according to these observers, arise either from arachnoid cells which have degenerated, or from the sclerotic connective tissue comprising the arachnoidal trabeculae.

Quite opposed to these views of the cellular origin of the smaller calcareous concretions are the observations of Arnold,<sup>1</sup> of Cornil and Ranvier,<sup>5</sup> of Mallory<sup>15</sup> and others. These observers have reported findings arguing for a vascular origin of the sand-like bodies. Arnold first noted a petrifying hyaline degeneration in the lumina of the smallest vessels in a psammoma. Somewhat similarly, Cornil and Ranvier observed phleboliths in the vessels of the choroid plexuses, identical in morphology and appearance with the granules known as brain sand. Mallory's description of calcification of the cerebral capillaries in the basilar nuclei also favors this idea of a vascular origin. One often sees, particularly along the course of the vessels in the granular layer of the cerebellum, small masses of hyaline which may lead to the occlusion of the vessels and often become calcareous. These formations, however, rarely are concentric, and there seems to be no relation between this process and the spherical and concentrically disposed psammoma bodies; and the same may be said of the irregular calcification of hyaline in gliomas. Mallory's conclusions that a vascular basis underlies the formation of these bodies surely cannot account for the depositions in non-vascular areas with which we are chiefly concerned. In short the stages in the formation of the calcareous deposits in the arachnoid indicated a cellular rather than a vascular origin for the primary infiltration. The vascular conception finds but little support except in the general appearances of the cellular whorls, for the membrane, though it carries vessels, is without capillaries and derives its nutrition from the circumambient cerebro-spinal fluid. In the

earliest stages the nuclei, almost to the exclusion of the cytoplasm, seem to be affected by the calcareous change. Whether this is due to the initial degeneration of the nuclear material or to a greater affinity of the lime salts for the degenerated nucleus, cannot be told.

*Observations on Osseous Deposits in the Arachnoid.*—The close association of the small calcareous depositions with the cells of the arachnoid membrane holds true also for the analogous areas of ossification in this membrane. Chemically, there seem to be "no essential differences between the processes involved in normal ossification and in most instances of pathological calcification" (Wells<sup>24</sup>), but biologically the latter appears to be degenerative and the former proliferative (Paulicki<sup>18</sup>).

The majority of the reports which deal with bone formation in the arachnoid describe the plaques in the spinal meninges, though there occur a few descriptions of growth of bone in the cerebral arachnoid (Fletcher,<sup>8</sup> Evans,<sup>7</sup> and others). As Virchow long ago pointed out in his justly celebrated lectures on tumors, these plaques were long erroneously regarded as the cause of epilepsy, chorea, tetanus, and other convulsive disorders.

It would seem that the process is more common in the membranes of the cord: at all events one encounters at operation small ossified bodies adherent to the spinal arachnoid more often than in the corresponding covering of the brain. One notable example, however, of ossification of the cerebral arachnoid has recently come under observation in a boy suffering with epilepsy. He had been the victim in early life of a severe infection, presumably a meningo-encephalitis, and at the operation, after an apparently normal dura had been reflected, the thickened arachnoid was found covered with large plaques of thin bone, some of which (shown in Fig. 8) were capable of being stripped away without causing bleeding. The minute spinal plaques which we have seen have likewise been deposited in membranes which had formerly been the seat of an inflammatory process.

In Fig. 9 is shown another example of bone deposition. This occurred as an osseous nodule in the falx of a patient who had a coincident pituitary tumor. More or less isolated nodules of this sort—really osteophytes—are not at all infrequent post-mortem findings and curiously enough, as has been long recognized, they are practically confined to the falx.

Still another example of true bone formation in the meshes of the human arachnoid is shown in Fig. 10. The coronal section includes the sagittal sinus at about the vertex and the wide-spread distribution of the deposits are apparent in the low-power drawing. They are of variable size; the largest is about 6 mm. in its long diameter and, as can be seen, it has served to displace the cortical tissue. The deposits are composed of true bone, as is evidenced by the occurrence in them of the typical lacunar systems, Haversian canals, and the characteristic osteoblasts and osteoclasts. Necessarily, they are vascularized, thus affording a marked distinction from the calcareous concretions which have already been discussed.



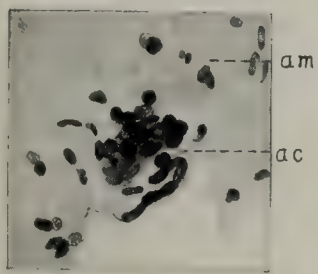


FIG. 1.

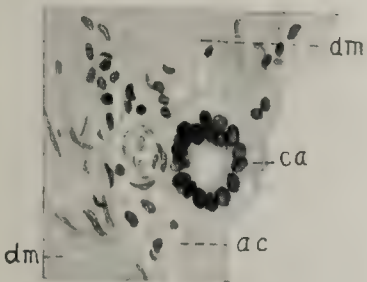


FIG. 3.

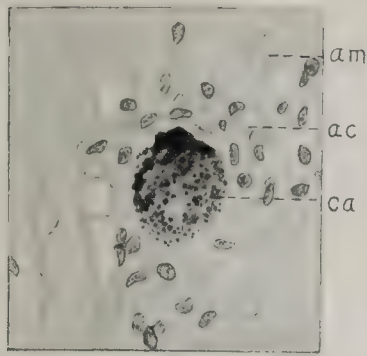


FIG. 4.

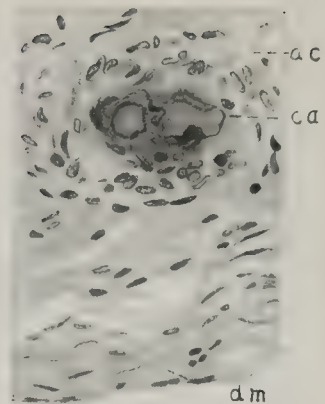


FIG. 5.

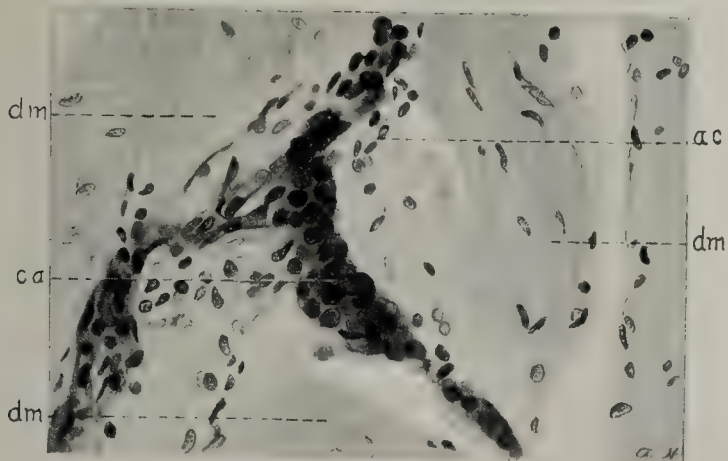


FIG. 2.

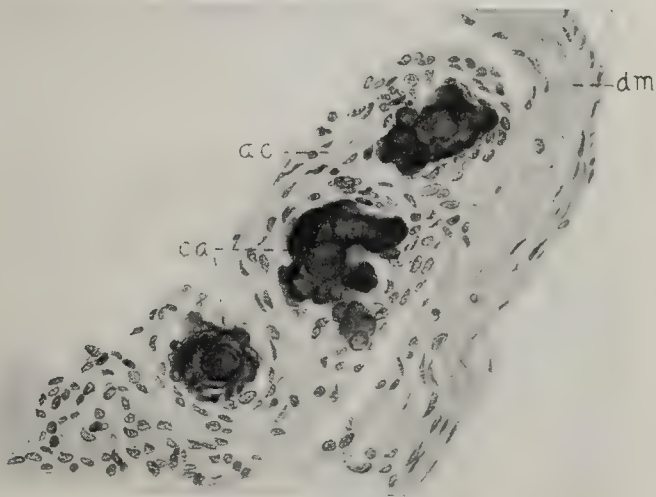


FIG. 6.



FIG. 7.



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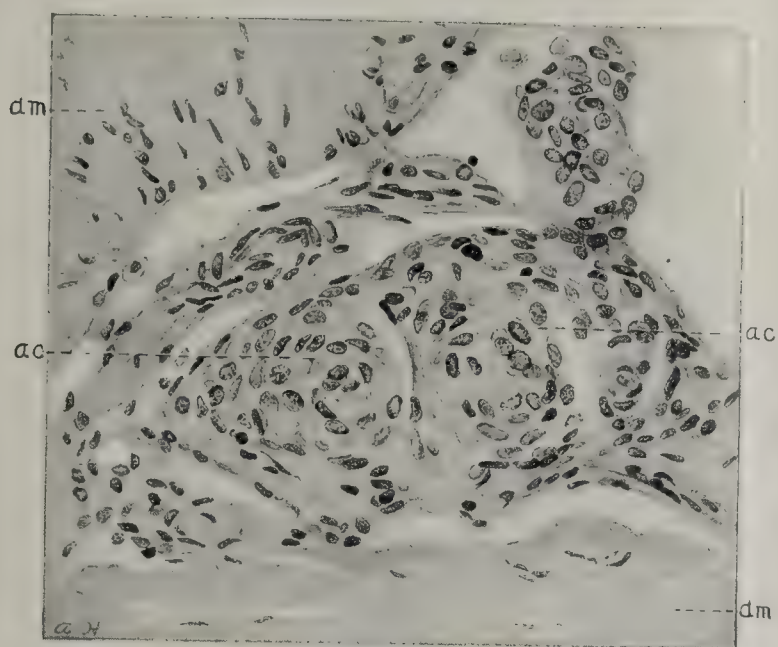


FIG. 7A.

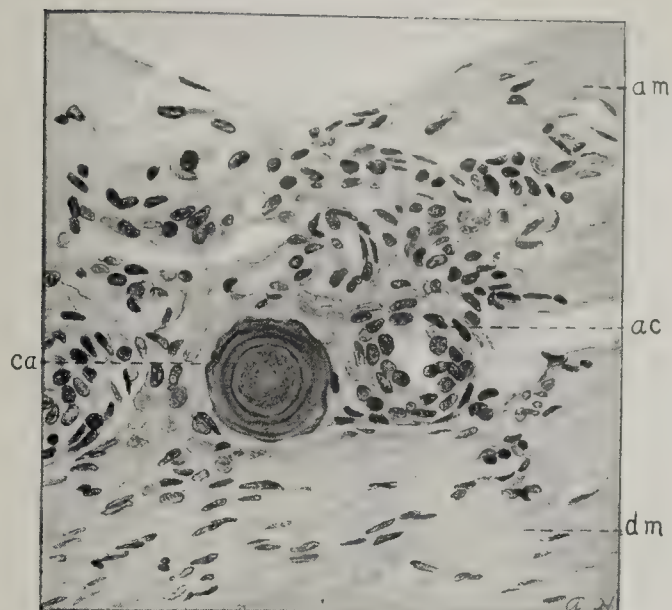


FIG. 7B.

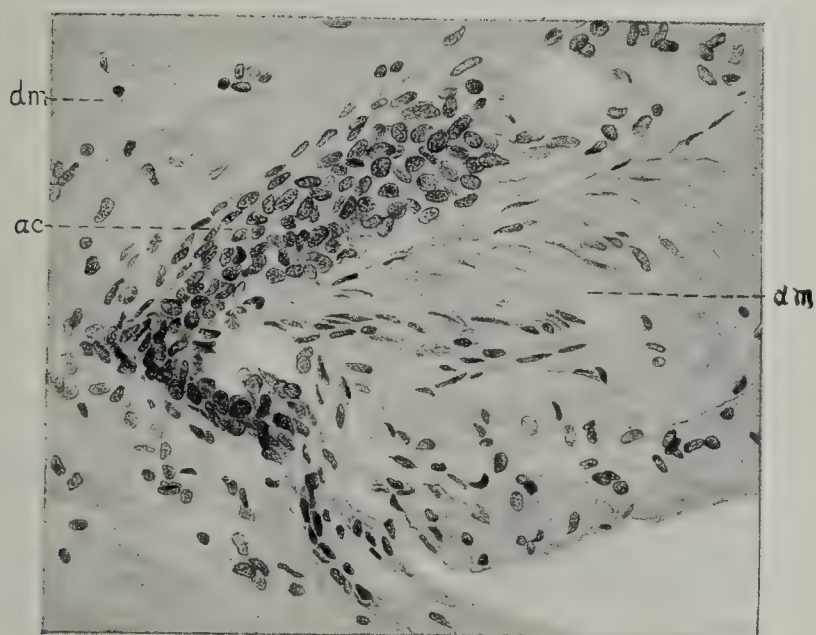


FIG. 7C.

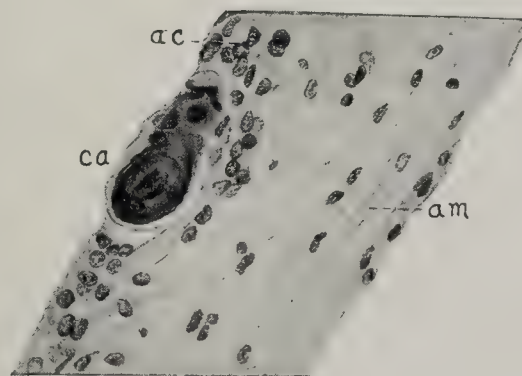


FIG. 7D.

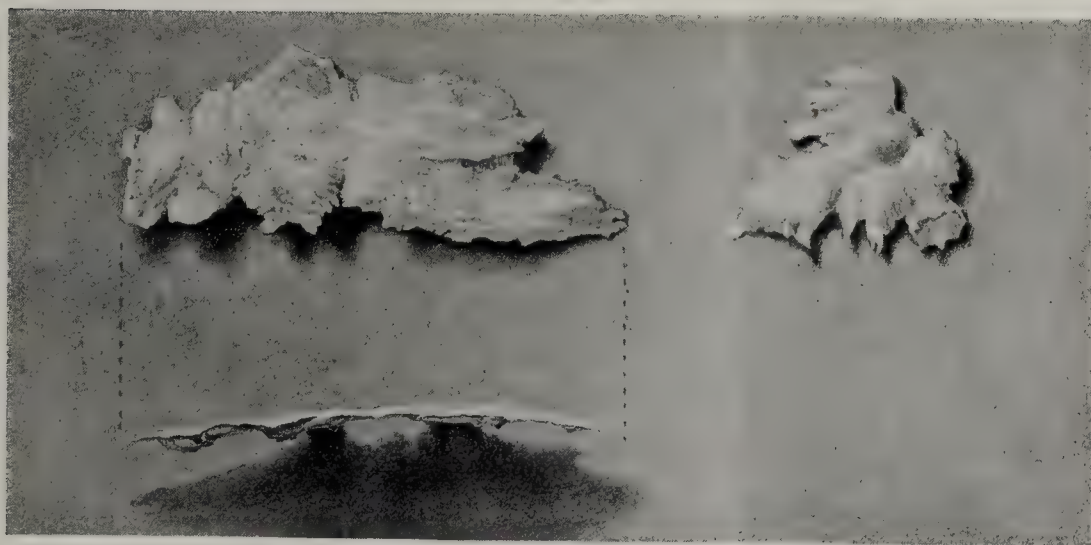


FIG. 8.

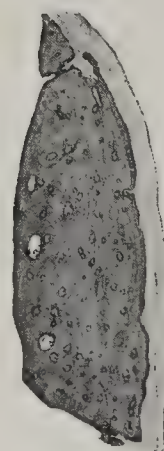


FIG. 9.



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FIG. 10.



FIG. 11.

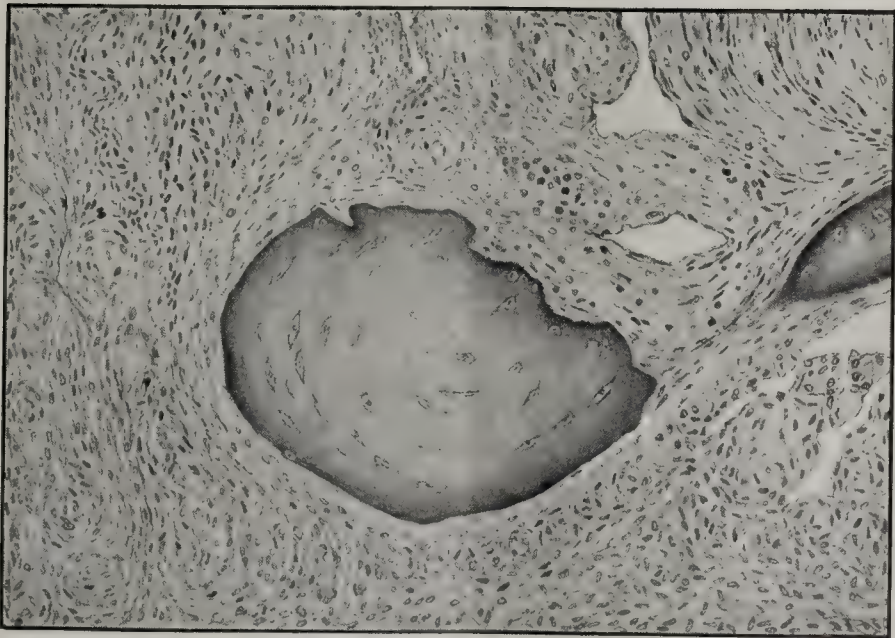


FIG. 12.



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One important feature of the osseous nodules lies in their relation to the surrounding tissue. In the low-power drawing (Fig. 10) the deposits appear to lie just beneath or within the dura, but under higher magnification (Fig. 11) the areas of bone are seen to lie in the midst of a very cellular mass. The general appearance of these cells, their situation and their relation to the surrounding dense strands of dural tissue mark them as undoubtedly arachnoidal in character. The hyperplastic appearance of these arachnoid cells, moreover, suggests in every way the cell clusters which were shown to be often associated with the calcareous bodies. It would, therefore, appear that, as the result of similar influences, the arachnoid may become involved in the two processes. Levi and Zanda have both described the cellular proliferation about the bony and calcified deposits in the spinal arachnoid, and it would seem that this is also to be found in the brain.

Whether this cellular hyperplasia of the arachnoid mesothelium is a precursor of the bone formation, or merely a secondary reactive phenomenon, is as difficult to decide as in the case of the calcareous deposits. Whether or not one is to be looked upon as a degenerative and the other as a proliferative process, the evidence on the whole suggests that the calcification and ossification depend on some underlying cause, which primarily or secondarily is accompanied by a proliferation of mesothelial cells.

These arachnoidal structures have the same histological ground-work which appears in the meningeal fibro-endotheliomas, and it is our impression that these tumors arise from the mesothelium of the arachnoid and not from the dura, as is commonly believed. The sections (Figs. 7 and 10) from the human brain were taken from cases in which there were a coincident fibro-endothelioma, and it is to be noted that in these mesothelial tumors, cellular whorls, psammoma bodies and true bone depositions, as shown in Fig. 11, frequently occur. This will be dwelt upon in further detail in a future communication.

#### SUMMARY.

Calcareous depositions in the form of psammoma bodies, or *corpora amylacea* of varying stages of development and of varying size, are of common occurrence in the arachnoidea of man and of the lower animals. Associated with this process of calcification there is apt to occur a hyperplasia of the arachnoidal mesothelium. The deposits of lime salts are apparently laid down in cell-bodies and in this membrane can bear no relation to the blood vessels.

The occurrence of true bone formation in the arachnoid of man should be regarded as a similar phenomenon, except that one may consider the process of ossification to be proliferative rather than degenerative.

The so-called dural endotheliomas show histologically the same cellular arrangements with calcareous and osseous depositions that are commonly found in the arachnoid and therefore take their origin in all probability from the mesothelium of this membrane.

#### KEY TO FIGURE LEGENDS.

ac=arachnoidal mesothelial cells  
am=arachnoid membrane  
br=brain  
ca=calcareous deposition  
dm=dura mater cerebri  
v=villus

#### DESCRIPTION OF PLATES.

FIG. 1.—Drawing of coronal section of the arachnoid membrane (am). In one area a clumping of nuclei is made out; many of these have undergone a degenerative change with infiltration of lime salts. In others, some of the intranuclear morphology is still retained. From a cat. ( $\times 315$  diam.)

FIG. 2.—Coronal section showing an arachnoid invagination (ca) within the dura (dm). The column of nuclei has undergone partial calcification. There is some deposition of lime salts in the inter-nuclear substance. On the periphery of this degeneration column, normal arachnoid nuclei (ac) are made out. From a dog. ( $\times 315$  diam.)

FIG. 3.—From a coronal section of a lateral wall of the superior longitudinal sinus of a cat. A portion of an arachnoidal cell-column or villus is shown surrounded by dural tissue (dm). A chain of oval arachnoidal nuclei appear, grouped around a small blood vessel. The arachnoid nuclei, arranged in one area in a circle, have become infiltrated with calcium salts (ca) and no longer show any intra-nuclear morphology. ( $\times 315$  diam.)

FIG. 4.—From a coronal section of a canine arachnoid membrane near the superior longitudinal sinus. In the midst of the delicate reticulum of the membrane (am) is a collection of typical arachnoid cells (ac) which surround a slight calcareous deposition (ca). ( $\times 315$  diam.)

FIG. 5.—From a coronal section: monkey. The dura (dm) shows its normal fibrous character. The arachnoid tuft consists of concentric layers of cells (ac), within which the characteristic infiltration with calcium salts is apparent. ( $\times 315$  diam.)

FIG. 6.—From a coronal section: dog. A cellular hyperplasia is everywhere in evidence in the arachnoid cells (ac); in some areas these cells surround masses in which calcareous infiltration (ca) has occurred. The dura (dm) is normal. ( $\times 315$  diam.)

FIG. 7.—From a coronal section showing the lateral wall of the superior longitudinal sinus with adjacent meninges and cortex cerebri, in the region of the fissure of Rolando. Note the invasion of the dense dural strands elsewhere by arachnoid structures in which calcareous depositions and cellular hyperplasias occur. From a man. ( $\times 60$  diam.)

FIG. 7A.—Higher magnification (315 diam.) of area A, in Fig. 7. The proliferation of arachnoidal cells (ac), arranged in concentric whorls, is shown in the midst of dense strands of dural connective tissue (dm).

FIG. 7B.—Higher magnification (315 diam.) of area B, in Fig. 7. In the midst of a collection of arachnoid nuclei is shown a psammoma body (ca), the internal structure of which resembles that of a starch granule. There is no cellular hyperplasia about the body, but in its immediate vicinity there is a typical whorl of arachnoid cells (ac). Surrounding the cellular area, the strands of dural tissue (dm) appear.

FIG. 7C.—Higher magnification (315 diam.) of area C, in Fig. 7. A marked collection of arachnoid cells (ac) is shown in the midst of the connective tissue strands of the dura mater.

FIG. 7D.—Higher magnification (315 diam.) of area D, in Fig. 7. A calcareous concretion (ca) occurs on the outer portion of the arachnoid membrane (am), with but slight proliferation of arachnoid cells (ac) about it.

FIG. 8.—Ossified plaques from the cerebral arachnoid of a man. (Normal size.)

FIG. 9.—Osteophyte from the falx of a man. ( $\times 10$  diam.)



FIG. 10.—Coronal section from a man showing multiple foci of bone formation in the arachnoid. From a patient with an endothelioma of the temporal region (cf. Fig. 12.)

FIG. 11.—Higher magnification of squared area in Fig. 10.

FIG. 12.—Meningeal endothelioma containing foci of ossification (cf. ossification of meninges elsewhere in the case Fig. 10). ( $\times 100$  diam.)

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## THE CALCIUM FACTOR IN HEMOPHILIA.

### A CASE WITH CALCIUM DEFICIENCY (CALCIPRIVA).\*

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(From the Research Laboratory of the Department of Health, New York.)

Ever since it has been known that calcium plays a significant part in the normal clotting of the blood, investigations have been carried out to determine whether a lack of this substance could account for the delay in coagulation in hemophilia and in other hemorrhagic diseases. The results of these investigations have led in general to the conclusion that a lack of calcium does not enter into the pathogenesis of hemophilia, and perhaps has little relation to this entire group of diseases.<sup>1 2</sup> The method pursued in such studies has been the simple one of adding a dilute solution of calcium to the blood and noting whether this addition shortened the clotting-time. The addition of calcium has been found not only not to hasten coagulation, but even to delay it. The present paper goes into this question of calcium deficiency somewhat more fully. We are able to report a case of hemophilia, in which the calcium was determined not only functionally by the simple method just mentioned, but also by means of a direct estimation of the

calcium of the blood, and a study of the calcium metabolism balance. In connection with this study we were able to pursue a similar investigation in a case of typical hemophilia. As far as we are aware, there have been no previous metabolism studies in this condition.

The child (Alter) is six years old and has been under our observation at the Hebrew Infant Asylum for the past three years. During the past year, and even longer, numerous coagulation tests of his blood have been made, and his general health has been carefully watched. Attention was first directed to him on account of his tendency to bleed from minor cuts, to manifest frequent "black and blue marks," and to have severe hemorrhages from the nose. As far as can be ascertained, he is the sole member of his family who is a bleeder, so that we must consider him as affording an instance of the sporadic type of hemophilia. He is fairly well nourished, weighs about fifty pounds and shows no other abnormality except a moderate degree of ichthyosis of the skin. This abnormality acquires additional interest owing to the fact that, like hemophilia, it is

\* The contents of this article form part of a paper presented before the Johns Hopkins Hospital Medical Society, April, 1915.



a disease which occurs in the male and is transmitted by the female. Color blindness, to which this law of heredity also applies, was not present.

When his blood was first tested in the spring of 1914, the plasma was found to take 58 minutes to clot. The normal clotting-time is from about six to ten minutes. For this test the method of Howell<sup>3</sup> was employed, which consists of adding one to five drops of a 0.5 per cent solution of calcium chloride to oxalated plasma. About one month later the plasma coagulated in 16 minutes. The variations in this regard during the past fifteen months, as may be seen from the accompanying table (Table 1), have been most marked. Recently, this summer, we

TABLE 1.—CLOTTING TIME OF PLASMA AND OF BLOOD. CALCIPRIVA CASE.

Date.	Plasma coag.-time.	Blood coag.-time (10 drops).	Remarks.
4-21-14	58 min.	29 min.	Control plasma clotted in 8 minutes.
5-21-14	16 min.	11.5 min.	Frequent nose-bleed. Hematoma over frontal bone.
5-23-14	30 min.	....	Plasma to which 6 drops of calcium were added clotted first.
5-26-14	28 min.	....	Tubes Nos. 5 and 6 clotted first. Nos. 1 and 2 did not clot.
5-28-14	28 min.	....	
6-15-14	22 min.	....	
6-25-14	18 min.	....	
8-19-14	12 min.	10 min.	Subcutaneous hemorrhages, and oozing from wound of finger.
8-24-14	12 min.	....	Calcium and magnesium have been given for metabolism tests.
8-31-14	12 min.	....	One drop of normal anti-thrombin permanently prevented blood from clotting, whereas control clotted in 10 minutes.
10- 7-14	....	19 min.	Bleeding from finger.
10-24-14	....	15 min.	
10-27-14	....	15 min.	Nose-bleed 48 hours ago.
11-10-14	32 min.	15 min.	Has received calcium for past 4 days.
11-17-14	34 min.	....	
12- 2-14	12 min.	7 min.	Has received calcium lactate for some weeks. Adding of calcium to blood postponed clotting, as it did also two weeks later.
6-26-15	88 min.	....	General condition not so good.
7- 2-15	60 min.	....	
7- 9-15	....	34 min.	12 drops of blood used. Addition of calcium reduced clotting-time to 13 minutes. Test reproduced in Table 1.
9- 8-15	22 min.		Platelets 516,000.

were surprised to find that the plasma once more clotted slowly, in fact that it had reached its lowest level, taking eighty-eight minutes to form a firm clot. In another column of this table will be seen the clotting-time of the unaltered blood—the period it took for ten drops of whole blood to form a clot in a clean vial having a diameter of 1.5 cm. We are unable to account for the marked variation in the coagulation time of the plasma. The hastening was not due to previous loss of blood, as is so commonly the case in hemophilia, but

seemed rather to run parallel to the general physical improvement of the child.

In view of the fact that at times, as may be noted, the plasma of this boy clotted almost within the normal limit, a characteristic of purpura in contradistinction to hemophilia, it may be questioned why we regard this case as an instance of hemophilia. In the first place, the coagulation time has occasionally been so greatly delayed that in this respect the case corresponded with one of hemophilia. Furthermore, a deficiency of blood platelets, the typical characteristic of purpura, was not found at any time; the counts at various intervals being 310,000, 487,000, 463,000. Increased pressure upon the blood vessels did not lead to the appearance of petechial hemorrhages as in purpura. This test which we have described elsewhere<sup>4</sup> as the “capillary resistance test,” consists in placing a tourniquet about the upper arm for a definite period, and noting whether this pressure leads to the appearance of petechiae upon the forearm. Again, the hemorrhages in this instance were fairly characteristic of hemophilia—they were large, not pinpoint, and occurred at times into the joints, for example, as hemarthros of the hip and of the ankle-joints. A consideration of these various phenomena would seem to justify our classifying the case as one of hemophilia.

In the course of a series of tests consisting of the addition of small amounts of calcium solution to the blood, we noted that this case reacted differently from those of other hemophiliacs,

TABLE 2.—EFFECT UPON CLOTTING-TIME OF ADDITION OF CALCIUM SOLUTION TO BLOOD. A. NORMAL CASE.

Clotting-time.	Control.	Drops of Ca solution added.			
		1	2	3	4
4 min.	+	....	+	+	+
5 min.	++	....	++	++	+
6 min.	+++	....	+++	++	++
7 min.	....	....	....	++	++
9 min.	....	....	....	++	++
11 min.	....	....	....	++	++
13 min.	....	....	....	++	++
15 min.	....	....	....	+++	++
17 min.	....	....	....	....	++

B. HEMOPHILIA CALCIPRIVA (ALTER).					
5 min.	—	—	—	—	—
9 min.	—	—	—	—	—
11 min.	—	+	++	—	—
13 min.	—	+	+++	+	—
17 min.	—	+++	....	++	+
21 min.	—	....	....	++	++
26 min.	+	....	....	+++	+++
34 min.	+++	....	....	....	....

C. TYPICAL HEMOPHILIA.					
4 min.	—	—	—	—	—
8 min.	—	—	—	—	—
10 min.	+	++	+	++	+
14 min.	++	++	++	++	++
18 min.	+++	++	++	++	++
22 min.	....	++	++	++	++
26 min.	....	++	+++	++	++
30 min.	....	....	....	+++	++

+++ denotes complete clotting-time.



in that coagulability was hastened by the calcium. In view of the quantitative determinations of the calcium of the blood, which will be considered below, we decided to make use of a solution of calcium chloride weaker than the 0.5 per cent commonly employed for recalcifying plasma, and accordingly prepared for this purpose a solution containing 0.04 gm. of CaO per 1000 parts of normal salt solution. This strength was selected because one drop corresponded approximately to the deficiency of calcium which had been ascertained to exist in the blood. An illustration of the results of adding this weak calcium solution to the blood may be seen in Table 2. It will be noted that the normal blood, which coagulated in six minutes, was not hastened by the calcium, that a case of typical hereditary hemophilia likewise remained unaffected, but that the blood of this boy (Alter, July 9, 1915) coagulated more than twice as rapidly upon the addition of the calcium. This result was repeatedly obtained, as may be seen in the remarks in Table 1; the only exception to this rule was in December, after he had been fed on calcium lactate for some weeks and his blood probably had absorbed its optimal amount of calcium.

A functional deficiency of calcium having been definitely established in this case, Dr Max Kahn tested the blood for its absolute content of calcium. For this purpose McCrudden's method<sup>5</sup> was employed, which enables one to determine the amount of calcium in even less than 10 cc. of blood. These determinations, which were made with from 6 to 10 cc. of blood aspirated directly from the vein, are reproduced in Table 3.

TABLE 3.—CAO IN BLOOD.

Normal controls.	Hemophilia calcipriva (Alter).	Hemophilia (typical).
0.072	0.047	0.068
0.068	0.056	0.069
0.074	0.058	.....
0.066	0.058	.....
0.071	*0.062	.....
0.073	*0.064	.....
0.062	.....	.....
0.068	.....	.....
0.075	.....	.....
0.069	.....	.....
0.075	.....	.....
0.065	.....	.....

\* Calcium lactate (2 gm.) had been given for the previous three days by mouth.

Although there is necessarily a certain degree of error associated with the examination of such a small quantity of blood, yet a comparison of the calcium content of this blood with that of normal and of typical hemophilic cases shows a difference quite beyond the range of error. The first examination of Alter, when he was in the poorest general condition, is most striking in this respect. It will be noted that the calcium increased when lime was given for a few days by mouth. At the time of this increase of blood calcium, the addition of calcium solution to the blood *in vitro* was no longer able to compass a hastening of coagulation. At another time calcium was given in daily doses of 2 grams for over a month, with the result that the coagulation-time was shortened. However, it never reached the normal, nor did the tendency to hemorrhage ab-

solutely cease, proving that a calcium deficiency was not the sole pathological factor in this case. An increase of antithrombin was not present to account for the hemorrhagic condition. A quantitative antithrombin test of this plasma may be found reproduced elsewhere in connection with the description of a new test for antithrombin.<sup>6</sup>

#### METABOLISM STUDY BY DR. MAX KAHN.

We were fortunate in being able to enlarge the scope of our investigation of this case (Alter) by a metabolism study, which, naturally, had as its primary object the determination of the calcium balance. At the same time a similar study was made of another child suffering from hemophilia, a boy of nine years (Julius) who, with his brother, had been under our observation for about two years. This boy was a typical example of hereditary hemophilia, so that the results in these two cases allow us to judge of the chemical processes not only in this atypical case but also in classical hemophilia. As far as we are aware there are no data of similar studies in this disorder to furnish a comparison.

Both patients were fed on a diet of milk, eggs, butter and bread. Duplicate samples of each substance given the patients were sent daily to the laboratory, where they were weighed and analyzed. The urine and the feces were collected daily for examination.

The experiment may be divided into three periods: (1) a fore-period, of a duration of three days, during which time the patients were kept in bed and fed the diet above mentioned, without being given any medication; (2) a calcium-feeding period, also lasting for three days, from August 19th to 22d, 1914 (during this time the patients received daily two grams of calcium chloride and one gram of magnesium oxide); (3) an after-period, lasting three days, during which time there was again no medication. The feces were demarcated, period from period, by means of carmine.

In the analysis of the food the following methods were employed. Nitrogen by the Kjeldahl method; total sulphur by the Wolff and Osterberg method, a modification of the Benedict method; calcium and magnesium by the McCrudden method, after ashing and extracting the ash with hydrochloric acid; phosphorus by the Neumann method.

In the urinary analysis, in addition, ammonia was determined by the Folin method, urea by the Benedict method and the total and ethereal sulphates by the Folin method. The inorganic sulphates were computed by subtracting the ethereal sulphates from the total sulphates, and the neutral by subtracting the total sulphate sulphur from the total sulphur. Total phosphorus was determined by the Neumann method, the phosphorus being weighed as magnesium pyrophosphate; creatine and creatinine by the Folin method; and uric acid by the Krueger-Schmidt method. For the feces the same methods were used. In the case of the fat the Kumagawa and Sato method was employed.

The results of the examinations are summarized in the four accompanying tables. (Tables 4, 5, 6, 7.) These show that



TABLE 4.—SUMMARY OF METABOLISM DURING THE THREE PERIODS.

A. TYPICAL HEMOPHILIA (JULIUS).

Substance.	Fore-period (average per diem).				Feeding-period (average per diem).				After-period (average per diem).			
	Food.	Urine.	Feces.	Bal.	Food.	Urine.	Feces.	Bal.	Food.	Urine.	Feces.	Bal.
Nitrogen....	16.14	10.55	3.75	+1.84	16.10	10.13	2.28	+3.69	14.61	10.38	1.93	+2.30
Sulphur.....	1.90	0.98	0.87	+0.05	1.93	0.91	0.95	+0.07	2.06	0.91	0.95	+0.20
Phosphorus...	3.78	2.13		+1.65	3.26	3.03		+0.23	3.79	2.51		+1.28
Chlorine.....	7.94	6.74		+1.20	9.19	8.17		+1.02	8.58	6.78		+1.80
Calcium.....	1.59	0.206	0.824	<b>+0.56</b>	3.39	0.466	2.08	<b>+0.85</b>	1.47	0.17	0.71	<b>+0.59</b>
Magnesium...	0.51	0.177	0.133	+0.20	1.64	0.84	0.61	+0.19	1.45	0.70	0.53	+0.22

B. HEMOPHILIA CALCIPRIVA (ALTER).

Nitrogen....	11.53	6.75	2.07	+2.71	11.50	6.99	2.17	+2.54	11.30	7.26	2.78	+1.26
Sulphur.....	1.31	0.88	0.30	+0.13	1.94	1.02	0.33	+0.59	1.84	0.95	0.29	+0.60
Phosphorus..	3.49	2.98		+0.51	3.36	3.09		+0.27	3.91	3.55		+0.36
Chlorine.....	4.60	4.09		+0.51	6.00	5.06		+0.94	5.03	3.44		+1.59
Calcium.....	1.37	0.39	1.80	<b>-0.82</b>	3.60	0.73	2.24	<b>+0.63</b>	1.33	0.21	0.81	<b>+0.31</b>
Magnesium...	0.42	0.19	0.11	+0.12	1.56	0.67	0.32	+0.57	0.67	0.14	0.07	+0.46

TABLE 5.—CALCIUM AND MAGNESIUM METABOLISM (ALTER).

CaO.					MgO.				
Day.	Intake.	Urine.	Feces.	Bal.	Intake.	Urine.	Feces.	Bal.	
Per'd 1.	1	1.35	0.37	1.73	<b>-0.75</b>	0.35	0.14	0.09	+0.12
	2	1.40	0.43	1.94	<b>-0.97</b>	0.47	0.21	0.12	+0.14
	3	1.37	0.39	1.71	<b>-0.72</b>	0.45	0.21	0.14	+0.10
Per'd 2.	4	3.55	0.72	2.31	<b>+0.52</b>	1.92	1.21	0.56	+0.15
	5	3.62	0.73	2.14	<b>+0.75</b>	1.35	0.42	0.21	+0.72
	6	3.65	0.75	2.28	<b>+0.62</b>	1.41	0.37	0.20	+0.84
Per'd 3.	7	1.32	0.12	0.46	<b>+0.74</b>	0.87	0.16	0.09	+0.62
	8	0.27	0.24	0.88	<b>+0.15</b>	0.62	0.10	0.05	+0.47
	9	1.42	0.27	1.11	<b>+0.04</b>	0.54	0.17	0.09	+0.28

During Period 2, calcium and magnesium were added to the food.

TABLE 6.—URINARY NITROGEN PARTITION.

A. HEMOPHILIA CALCIPRIVA (ALTER).

Day.	Amount cc.	Total N. gm.	Urea % Total N.	Ammonia % Total N.	Creatinin % Total N.	Uric Acid % Total N.
1	750	10.56	82.7	4.2	3.1	2.25
2	720	9.87	83.4	4.4	3.4	1.98
3	810	11.23	82.5	3.9	2.9	2.72
4	690	10.07	82.9	3.9	3.2	2.15
5	760	10.11	82.7	4.1	3.1	2.22
6	770	10.27	83.2	4.3	3.2	2.14
7	840	9.87	83.5	3.8	3.4	2.07
8	720	10.56	81.9	4.4	3.3	2.24
9	730	10.72	82.8	4.2	3.4	2.05

B. TYPICAL HEMOPHILIA (JULIUS).

1	450	6.78	82.7	4.2	3.5	1.2
2	530	7.18	83.8	4.4	3.4	1.4
3	470	6.27	83.6	3.9	3.7	1.4
4	490	6.86	85.2	4.3	3.4	1.3
5	520	7.02	82.9	4.4	3.1	1.5
6	580	7.10	84.4	4.1	3.6	1.2
7	620	—	—	—	—	—
8	490	—	—	—	—	—
9	510	7.26	82.8	4.2	3.5	1.2

TABLE 7.—SULPHUR OUTPUT IN URINE AND FECES.

A. HEMOPHILIA CALCIPRIVA (ALTER).

Day.	Urine.				Feces.
	Total S. gm.	Ethereal SO <sub>4</sub> % Total S.	Inorganic SO <sub>4</sub> % Total S.	Neutral % Total S.	Total S. gm.
1	0.82	12.6	72.9	14.5	0.27
2	0.97	14.2	70.1	15.7	0.32
3	0.85	13.7	72.0	14.3	0.31
4	0.89	12.9	69.9	17.2	0.38
5	1.02	12.4	75.0	12.6	0.29
6	1.15	12.2	74.7	13.1	0.33
7	—	—	—	—	0.27
8	—	—	—	—	0.28
9	0.95	13.4	71.1	15.5	0.31
Average	0.95	13.0	72.2	14.7	0.31

B. TYPICAL HEMOPHILIA (JULIUS).

1	0.97	14.3	68.1	17.6	—
2	0.92	14.5	69.2	16.3	—
3	1.05	16.2	65.7	18.1	0.87
4	0.97	12.9	67.9	19.2	0.98
5	0.86	16.1	68.4	18.5	0.85
6	0.89	14.4	68.0	17.6	1.04
7	0.87	14.7	69.0	16.3	0.95
8	0.91	13.8	70.6	18.6	0.90
9	0.94	13.2	69.2	17.6	1.02
Average	0.93	14.3	68.3	17.3	0.94

the disturbances of nutrition are not at all similar in the two children. In both, however, the nitrogen metabolism, the sulphur, and phosphorus partitions and determinations, appeared to be normal. A positive balance is observed in every instance and the output of the various fractions fall within normal limits. The chloride and the fat exchange also seemed undisturbed.

When we turn to the mineral metabolism we find radical abnormalities in the case of Alter, whereas the exchange of lime in the boy with typical hemophilia appears to be normal (Tables 4 and 5). It will be observed from the summary given in Table 5 that the calcium balance of Alter was negative, and that it promptly became positive when lime was added to the diet; in the after-period the retention of lime became increasingly less day by day.

GENERAL CONCLUSIONS.

Typical hereditary hemophilia is not associated with a deficiency of calcium. Our investigations showed, as had others previously, that the addition of calcium to the blood *in vitro* delays rather than hastens coagulation. Furthermore, a deficiency could not be established by quantitative determinations of the calcium in the blood, and a metabolism study showed that the exchange of lime salts, as well as of numerous other inorganic as well as organic substances, differed in no way from normal.

Hemophilia, however, does not seem to be a sharply circumscribed entity, if we group under hemophilia disorders characterized by the three main criteria of this disease: delayed clotting of the blood, a normal number of platelets, and a negative "capillary resistance test." If we demand that the



defect be hereditary, it is possible that no variation in type will be found. The atypical instance which we have studied was of the sporadic variety, but had all the other symptoms of classical hemophilia and therefore cannot be considered as a case of purpura. This boy showed a definite deficiency in the calcium of the blood from a functional point of view, the addition of a weak solution of calcium markedly hastened the clotting of the blood. Quantitative determinations of blood calcium also showed a deficiency compared with the normal. In addition, a study of his general metabolism brought out the fact that there was a negative balance of lime, which became positive when lime salts were added to the diet. Although we do not wish to

make the conception of hemophilia more complex, or to burden its nomenclature, it would seem that this instance must be considered a distinctive type of this disorder, an instance of calcium deficiency or a *hemophilia calcipriva*.

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BACTERIOLOGICAL RESULTS IN CHRONIC LEUKÆMIA AND IN PSEUDOLEUKÆMIA.<sup>1</sup>

By C. H. BUNTING, Madison, Wis., and J. L. YATES, Milwaukee, Wis.

In a recent article Simon and Judd (Jour. Amer. Med. Asso., 1915, LXIV, 1630) report the cultivation of a diphtheroid organism similar to that found in Hodgkin's disease from the lymph-glands of a case of acute leukæmia, confirming the findings of Steele in a similar case (Boston Med. and Surg. Jour., 1914, CLXX, 123). Although the authors make no strong claim for the etiological significance of their finding, they suggest that the occurrence of the same organism in two cases must be more than fortuitous and emphasize the necessity of further investigations in this group of diseases.

It is with this in mind that we desire to report our bacteriological investigation of two recent cases. The first of these was a case of chronic lymphatic leukæmia of two years' duration, seen by the courtesy of Dr. A. W. Gray, of Milwaukee; and the second was a case of acute lymphosarcoma (or pseudoleukæmia) referred by the Jackson Clinic, of Madison, Wis.

Dr. Gray has kindly furnished the following clinical notes of the first case:

Jan. 18, 1913. W. H. M., male, white; traveling salesman; aged 40.

Family History.—Negative.

Past History.—Childhood diseases and frequent attacks of tonsillitis; tonsils always large. The laryngologist at the Mayo Clinic removed adenoids two years ago. The patient cannot remember whether or not the glands in the neck were enlarged at the time the tonsils were removed, in fact he had not noticed the enlargement until his attention was called to it during the examination.

Present Condition.—Cold in the head, deafness and aphonia.

Examination.—Fairly well nourished, weight 140 pounds. Heart and lungs negative; spleen palpable; pharynx, fauces and vault of mouth show a peculiar red color which does not suggest acute inflammation; granular pharyngitis marked; fragments of tonsillar tissue present; faucial tonsil large; cervical, axillary and inguinal glands markedly enlarged, especially the anterior cervical, many of which were about the size of a hazel-nut. The blood examination showed the leucocyte count to be 186,000. A differential count was not made at this time. Hæmoglobin, 85% (Sahli).

<sup>1</sup> This work has been aided by a grant from the Rockefeller Institute for Medical Research.

The patient was under active treatment from February 1, 1913, when the leucocyte count was 175,200. He was given benzol in varying doses. Roentgen-ray radiation was given by Dr. O. H. Foerster. The leucocyte count, on March 29, 1913, had dropped to 8200. Sodium cacodylate, gr.  $\frac{3}{4}$ , hypodermically, was given at this time once in two days for two or three weeks. There was a decided subsidence of the glandular enlargements during this period, and an almost complete disappearance of the posterior and anterior cervical glands followed the removal of adenoids by Dr. H. B. Hitz on June 26, 1913. Roentgen-ray treatments, benzol and sodium cacodylate have been given as seemed indicated. In general the patient's condition has remained fair during the two years that he has remained under observation. His principal complaint during this time has been lack of endurance and a feeling of weakness, but he has continued at his work whenever active treatments did not interfere. At times he has complained of pleuritic-like pains through the chest which either subsided without special treatment or seemed to disappear after X-ray treatment.

The following counts have been made in his case:

Date.	W. b. c.	Neutr. %	Eos. %	Bas. %	S. Lymph. %	L. Mono. %	Trans. %
II-18-13.....	175,000	48.8	0.0	1.2	7.5	32.5	10.0
III-29-13.....	8,000	66.0	0.0	0.0	5.4	20.6	8.0
IV-17-13.....	6,200	94.5	1.0	0.0	2.0	1.5	1.0
V-24-13.....	6,200	40.0	1.0	0.0	56.5	2.0	0.5
VI- 3-13.....	6,200	41.5	0.5	0.0	48.5	8.0	1.5
VII-21-13.....	7,080	28.0	0.67	0.0	50.7	19.3	1.33
VIII-25-13.....	10,000	26.0	1.33	0.0	44.0	27.0	1.67
IX-22-13.....	10,100	20.0	1.5	0.0	35.0	40.0	3.5
X-13-13.....	15,000	23.0	3.0	0.0	43.0	29.0	2.0
X-23-13.....	6,800	35.1	1.3	0.0	56.0	2.6	4.0
XI-25-13.....	8,800	14.5	0.4	0.0	82.3	1.0	1.8
IV-20-14.....	21,200	15.75	0.75	0.0	81.75	0.5	1.25
V- 7-14.....	15,600	16.0	3.0	0.0	74.0	1.0	6.0
VII- 7-14.....	13,100	15.0	0.5	0.0	81.5	2.5	0.5
IX-18-14.....	14,800	13.0	1.0	0.0	61.0	2.0	23.0
XII-30-14.....	25,500	5.5	0.5	0.0	90.0	0.5	3.5
I- 1-15.....	41,000	3.0	0.0	0.0	96.0	0.0	1.0
III- 2-15.....	63,200	3.5	0.0	0.0	55.0	41.5	0.0
III-31-15.....	92,900	....	....	....	....	....	....
IV-16-15.....	99,400	....	....	....	....	....	....
IV-26-15.....	161,200	....	....	....	....	....	....
V- 8-15.....	92,000	....	....	....	....	....	....
V-19-15.....	65,400	....	....	....	....	....	....



Blood smears from this case examined on March 5, 1915, when the leucocyte count was 60,000, showed 3% of polymorphonuclear neutrophils and 97% lymphocytes, of which 11% might be classified as large lymphocytes. On March 25 a group of glands was removed from the left axilla under the strictest aseptic precautions. The group was thoroughly flamed in a Bunsen burner and then incised and portions of the tissue were planted upon a variety of media, chiefly blood-serum and egg-medium. Some of the tubes thus planted were incubated aëroically, some anaëroically and still others under paraffin seal.

Of these inoculations six tubes remained sterile; four tubes showed a white coccus, one a white coccus and a diphtheroid organism, and one tube a pure culture of a diphtheroid organism, which grew apparently only upon the gland substance itself. By gradual transfers of gland substance, this diphtheroid was finally induced to grow upon Loeffler blood-serum, although at the time of writing it does not grow confluent, but as minute discrete colonies of a glistening whitish appearance. In stained smears it appears chiefly as a banded organism with marked tendency to the development of the clubbed forms. Coccoid forms are present, but the bacillary forms predominate. Morphologically it is identical with the strains isolated from cases of Hodgkin's disease. In its difficulty of cultivation upon artificial media, it resembles closely an organism grown by us from a case we designated "chloroma" because of greenish orbital tumors in addition to general glandular enlargement. Histologically the glands of the two cases are of almost identical appearance in their loss of architecture and diffuse infiltration with small lymphoid cells.

The second case studied presented clinically the appearance of a case of acute leukæmia, in the character of the mouth lesions, in the enlargement of certain cervical glands, and in the presence of cutaneous and subcutaneous tumors. However, blood counts during April and May have shown a leukopenia (5000-6000) with the following differential picture:

	Neut. %	Eos. %	Bas. %	Lymphocytes %	Trans. %
April 15, 1915, 6000..	70.5	0.5	1.0	21.0	7.0
May 17, 1915, 5000..	63.5	1.5	0.5	25.0	9.5
May 22, 1915, 5600..	76.0	0.5	0.5	17.5	5.5

The history of the case is as follows:

April 14, 1915. A. K., aet. 52. Farmer.

*Complaint.*—Glandular enlargements in neck and groins.

*Family and Past History.*—Unimportant.

*Present Illness.*—Eight months ago after extraction of an ulcerated tooth he noted beginning enlargements in the glands beneath the jaw, which progressed and extended to the other side of the neck and to both groins. Later there appeared cutaneous and subcutaneous nodules, some becoming dark in color. Four months ago the gums began to hypertrophy sufficiently to override the teeth.

He has continued to work, but has noted dyspnoea and palpitation after continued exertion.

*Physical Examination.*—A well nourished, muscular man, of good color. Skin soft and moist. There is a very extensive general lymphatic glandular enlargement with an involvement of the subcutaneous tissue leading to skin changes.

*Lymphatic Glands.*—Both triangles on both sides of the neck are quite completely filled with nodules varying in size from a cherry-pit to a walnut. In the lower parts these enlarged glands are discrete and movable; above they are matted together and fixed to the surrounding structures, particularly in the submaxillary region, where they seem to be almost subperiosteal. A few have become attached to the skin. Supra-orbital and pre-auricular enlargements are absent. Chains of glands can be felt extending downward on either side of the spine from the suboccipital region.

The left tonsil is distinctly hypertrophic. The submucous adenoid tissue, particularly on the left side, is so enlarged as to make the articulating surfaces of the teeth sink below the level of the gums. There is no distinct glandular enlargement at the base of the tongue. Marked pyorrhœa, caries and dribbling of saliva are present.

Both axillæ contain a few large glands and extending from these downward on to the sides of the chest and forward and upward in front of the pectoral muscles are chains of glands. These are attached deeply and the overlying skin is freely movable, giving an impression that the lymphatics leading into the thorax have been involved, though substernal distress is not manifest, nor are the superficial veins dilated.

Both brachial chains are enlarged above the epitrochlears. The inguinals are considerably enlarged but discrete and movable. Some glands above Poupart's ligament are palpable.

The liver and spleen are both impalpable and neither show enlargement on percussion. No ascites is detected.

The skin involvement is wide-spread from the forehead to the middle of the legs. These lesions seem to be of the progressive type, starting as subepithelial nodules, not tender or discolored. The epithelium wrinkles over these early nodules and when they are depressed assumes a pigskin appearance. Later reddening occurs and finally a dull purplish color develops. Now the epithelium has become adherent and looks like grain-leather. At times regression occurs in these nodules, leaving behind a macular-like discoloration. Ulceration has not occurred; no itching nor discomfort other than mechanical has been noted.

On April 15 Dr. R. H. Jackson excised a cutaneous nodule for culture and for histological examination. The cultures from this nodule resulted in the growth of a white coccus in three tubes and of a slow-growing diphtheroid and a rapid-growing coccus in a fourth. An attempt to isolate the diphtheroid failed.

On May 22 a second skin nodule was excised. The skin surface was seared in a Bunsen flame and the tissue dissected off from the under side of the nodule for culture.

This second attempt resulted in the growth of a diphtheroid in four tubes, a coccus in one, and no growth in five tubes. The organism is morphologically like that found in the previous case, yet grows somewhat more freely upon artificial media. Its cultural characteristics have not yet been determined.

Histologically the skin nodule shows a diffuse infiltration, of the corium and subcutaneous tissue, by cells of the large mononuclear type, similar to those seen in the blood in acute leukæmia and those found in the lesions of lymphosarcoma. As in lymphosarcoma there appears to be no destruction of the infiltrated tissue. There is a slight fibroblastic stimulation.

The etiological relationship of this diphtheroid organism to the diseases described must perhaps remain for a time *sub judice*. The occurrence of similar organisms in a variety of diseases would certainly seem to be an argument against their etiological importance. However, it is our experience thus far that this type of organism is found with readiness only in one general group of apparently related diseases and in these without fail with good technique. In this group we would include Hodgkin's disease, the lymphogenous leukæmias, the pseudoleukæmias (lymphosarcoma), Banti's disease and probably also mycosis fungoides. Outside of this group, if the organism is found, there is also some histological evidence of its activity.



# ICONOGRAPHIC NOTES ON GIROLAMO FRACASTORO.<sup>1</sup>

By ARNOLD C. KLEBS, M. D.

The name of Fracastoro appeals with peculiar emphasis to us medical men in the present-day development of our science. Fracastoro's contemporaries saw in him, as we still do, the erudite scholar and elegant poet, the ingenious interpreter of some of nature's secrets (in the heavens as well as on earth), the physician as well as the friend of the highest of his time, a kind helper to the humble and an inspiring teacher of the young. But to us he is still more; his work marks a new era in medicine, the era of bacteriology which has brought about in our generation far-reaching results, not only in our etiologic conceptions, but also in their prophylactic application. It has taken three hundred years to recognize the fundamental significance of Fracastoro's teachings; and when we now read in the transactions of learned societies, in the journals of the sixties, the discussions about the early attempts at correlating certain diseases with the minute organisms then discovered, and note the profound scepticism and even derision with which they were received on all sides, we must wonder, indeed, that similar conceptions could have arisen three centuries ago. And this is exactly what happened in Fracastoro's case. Call it intuition, anticipation, guess-work or what not, the fact remains that his idea had immense potentiality. It makes one realize that ideas of men of genius, however little their significance may be understood at the time, always merit respectful attention—a further plea for the cultivation of historical studies in medicine.

The earliest, most primitive idea, that disease is the result of some harmful agent entering the body from without, was curiously enough not taken up by the school of medicine of more advanced eras. Almost all maladies were explained as internal disharmonies, or the corruption of the fluids and solids composing the body. Only towards the end of the middle ages did the idea of the rôle of infection begin to find advocates. Here Fracastoro made one great step in advance, at least in the light of our present-day conceptions, which we must always guard ourselves from considering as final. He not only insisted on the external origin of certain diseases, but came to the logical conclusion that the foreign bodies, the "seminaria," or seeds, imperceptibly invading the organism, must possess qualities of life and reproduction, and that, therefore, disease produced in this way must become transmissible from the sick to the healthy. He was aware—and stated it with unprecedented clearness—that this transmission could take place by direct contact, through the air or infected objects, the "fomites," an idea which, as I have shown elsewhere,<sup>2</sup> had already been expressed in a verse of the School of Salerno. This idea of an animate contagion we find for the first time painstakingly analysed as to its significance and practical consequence in Fracastoro's work. The various infectious diseases are de-

scribed and explained on this basis; phthisis, for instance, is for the first time definitely placed among them. What a fund of minute observation and lucid discrimination do we find; for example, in that chapter on the fevers called "lenticular or puncticular," in which we unmistakably recognize the first description of typhus.<sup>3</sup> Fracastoro's *De contagione et contagiosis morbis* (published in Verona in 1546), in which all these advanced conceptions are to be found, undoubtedly marks the beginning of the scientific investigations of infectious diseases. It is of much deeper meaning to us than his other great work upon which rests his wider fame among his contemporaries.

This work, a poem, in form modelled after the Georgics of Virgil, in substance treating of that strange disease which from the time of the French siege of Naples, under the name *morbus gallicus*, or *mal franzoso*, attracted the keenest and most interested attention of Fracastoro's contemporaries. To us this poem is interesting, chiefly because its hero, the shepherd *Syphilus*, has given his unprejudicial name to this malady for times to come. Fracastoro has left us other contributions, bearing the imprint of far-seeing genius. They have, not long ago, been discussed and analyzed most charmingly by Dr. Osler, so that our passing allusion to his greatest work may here suffice.

Of the external circumstances of Fracastoro's long life (1483-1553), we also possess several excellent accounts. Born in Verona, he belonged to a distinguished patrician family. Even in the 13th century one of his ancestors, Aventino, had attained fame as the physician of Can Grande I, that mighty condottiere and patron of the arts and letters, as testified by his friend Dante. Little known is the handsome canopied tomb of this Fracastoro on the façade of S. Fermo Maggiore, before which our Girolamo surely had often passed. Up to 1508 we find Fracastoro studying and teaching at the University of Padua, which was closed in that year because of war. Later he passes through Pordenone, and finally settles near Verona on his farm at the foot of Monte Baldo, whence he could overlook Lake Garda and Catullus' Sirmio and the towers of his native town rising out of the wide, fertile Lombard plain. As a true Cinquecento scholar his interests were manifold and by no means confined to medicine. He was at home in mathematics, astronomy, geology, philosophy; enjoyed and cultivated poetry and music. In our time of specialism, such universal proficiency is difficult to comprehend, but among learned men of that day it was rather the rule than the exception. Fracastoro, himself, as also his biographers, gives us the names of his numerous friends and associates. Many of the best of his time are among them. Among physicians we know of his close association with the dalla Torre family, also from Verona; the father, Girolamo,

<sup>1</sup> Read before the Medical and Chirurgical Faculty of Maryland, Baltimore, June 16, 1915.

<sup>2</sup> The Johns Hopkins Hosp. Bull., 1913, XXIV, 70.

<sup>3</sup> Imported from Cyprus and the neighboring isles into Italy in the years 1505 and 1528.



was his teacher in practical medicine in Padua, and intimate friendship bound him also to the younger dalla Torre, Marc Antonio, the friend and anatomical co-worker of Leonardo da Vinci. Others were G. Cesare Scaliger, Gianbattista Montanus, Aloisio Mundella, to mention only a few. Whether his practice as a physician was very extensive we do not know, but undoubtedly he gained much experience in several of the epidemics which ravaged Italy, and on the battlefields in the Venetian army under Bartolomeo Lavinio. Among his many prominent patients we know of Pope Paul III and Caterina de' Medici.

Fracastoro's earliest biographer, an anonymous author, probably a contemporary, gives a description of his external appearance: "Of low though sturdy build, broad shouldered, with handsome beard, black, abundant hair, round face, dark eyes, the nose short and turned upwards by his frequent contemplation of the stars; serenity and ingenuity of mind mirrored in his features." Mencken, to whom we owe the most extensive biography of Fracastoro, adopts this description in general, but does not fail to see the absurdity of the peculiar deformation of the nose and its cause. "Woe unto ye astronomers," he exclaims, "if the stars thus endanger your noses"! This description, we may safely conclude, gives us but scant and not very reliable information on the subject. We must, therefore, turn to extant portraits. A great number exist, but for us only those can be of interest which were most probably made from life. Upon careful examination, we find that the majority were done after Fracastoro's death from the very few likenesses we know to have been made during his lifetime. I have searched in Verona and Padua for a contemporary painting of him which was said to exist, but I have been unable to find anything that could be identified with certainty. In the Museo Civico in Verona two canvases were pointed out to me as possibly representing Fracastoro. One is in a group, by Turbido: an old man with white hair and beard sitting in the foreground is evidently painted as a portrait. The painting is in very bad condition and cannot be used for identification without better information about its origin, which is shrouded in complete mystery. The other is a portrait, attributed to Titian, of a man between 50 and 60 years of age. It depicts a forceful man of action, a statesman or great noble, rather than a contemplative scholar. A golden chain around his neck also speaks for this view. If we put these two paintings aside as very doubtful likenesses of Fracastoro, there remains, as far as I know, only one engraving, a wood-cut, which represents him as he really was. It appears as frontispiece to Fracastoro's astronomical work "*de Homocentricis*," which was published in Verona in 1538. This portrait has evidently served as prototype for the swarm of likenesses which appeared later. An excellent reproduction of this portrait is given in Garrison's "*Introduction to the History of Medicine*" (Philadelphia, 1914), so that it is not necessary to repeat it here. Fracastoro, at the time of the publication of this work in or near Verona, was about 50 years old, and it seems very probable that he sat for the frontispiece destined for his book. We do not know the artist, but this portrait

speaks for his mastery of technique. Without hesitation and apparent attempt at idealization, he has drawn a strong, realistic likeness. The dark eyes, rather far apart and deep-seated, looking out into the distance, the slightly curved nose with a small wart on the right side, the firmly closed mouth and straight lower lip, the square form of face with prominent cheekbones, the broad, slightly receding forehead and skull discernible under the abundant long hair of head and beard, all that we feel the artist drew as he saw it before him. The pose is three-quarter face and Fracastoro wears a three-horned biretta, a wide-sleeved coat with fur collar, ruffled cuff, and in his right hand, of which the index finger carries a ring with a large oval stone or seal, he holds an armillary sphere and a laurel sprig, insignia which have been usually repeated in the later reproductions.

There are two other contemporary portraits of Fracastoro which are undoubtedly intended to represent him. They are bas-reliefs showing him in profile and, I believe, are both inspired by the drawing of the wood-cut just described, although I am unable to prove this conclusively. The more important is a large medallion in bronze which was made about 1551 by Giovanni Cavino,<sup>4</sup> the renowned medallist of Padua, on the order of Gianbattista Ramusio, then Secretary of the City Council, and placed with a similar medallion, also by Cavino, of Fracastoro's and Ramusio's friend, Andrea Navagero, at the Porta San Benedetto in Padua. This medallion is now in the Museo Civico of Padua, where I have examined and photographed it. It gives only the relief of the head in profile, surrounded by the name. The modelling is good, but bears the stamp of conventionality and idealization. It does not bring out any salient, characteristic features. The head is uncovered, showing the shape of the skull. It may be held that it represents an older man than the wood-cut, more nearly the age of 67, which Fracastoro had about reached when this work was executed and that, therefore, Fracastoro might well have posed for it. For various reasons, which it would take too long to enumerate, I believe that this relief is nothing more than a conventional representation of Fracastoro, and not an authentic likeness. The same, I believe, is equally true of the second profile, also in bronze on a smaller medal, attributed to Giulio dalla Torre (a learned professor of the law in Padua, and younger brother of Marc Antonio). This medal may not be genuine at all, as some (*e. g.* Friedlaender) think; at any rate it is a charming piece of work, though more likely taken from the wood-cut than from life. Neither one of these reliefs, therefore, helps us to visualize clearly Fracastoro's features.

Well known, perhaps better than any of the portraits described, is the Fracastoro statue in Verona. Standing on the Piazza dei Signori, with his back against the Palazzo della Ragione, one faces the statue of Dante, and behind it rises the charming Renaissance building, the Palazzo del Consiglio, adorned with the statues of five famous Veronese, the younger

<sup>4</sup> Cavino was also a very clever imitator of the medals representing Roman Emperors, a fact which has given much trouble to modern numismatists.



Pliny, Cornelius Nepos, Macer, Catullus and Vitruvius. It adjoins a narrow street, over which spans a graceful stone arch. Upon this, high up on a pedestal, too high for close examination, is placed this marble statue of Fracastoro. The pedestal bears the legend:

HIER · FRACASTORIO ·  
PAVLLI · PHILIPPI · F ·  
EX · PVBLICA · AVCTORITATE ·  
DICATA  
AN · SAL · MDLIX ·

The artist has represented Fracastoro erect, above life size, draped in a long, antique toga, the head slightly inclined forward and to the left, the right arm bent at a right angle, the hand holding a globe, the left arm hanging at his side. The features seem to belong to a man older than the one in the wood-cut; the full beard and the hair of the head are more abundant than in the other portraits. Otherwise there is an unmistakable similarity of feature, especially to those of the Cavino head. The decree of the Senate which provided for the erection of this statue is dated 1555, and it seems that in that year it was put up somewhere in the Piazza d'Erbe, to be transferred later, possibly in 1559, the date of the epigraph, to the place it now occupies. The documents mention as the artist of this statue: "*Danesium Cataneum Carriensem ex Lunense agro.*"

An interesting feature of this statue is that the artist who carved it seems to have also done the bronze bust of which a reproduction is here given. So far as I am aware, it has not appeared in medical publications. Danese Cataneo was sculptor, architect and poet, a pupil of the famous Sansovino and closely connected with that group of men which Fracastoro frequented and among whom Tasso was his close friend. We find many fine examples of his work in the Venetian provinces. It is characterized by certain distinct features of realistic treatment which aid in its identification. The bronze bust before us, since 1827 in the Imperial Museum of Vienna, has only recently been recognized as Cataneo's work. For a long time it stood in the museum, not much noticed, as the work of an anonymous artist, after which it was for a time thought to have come from the studio of Alessandro Vittorio, until finally more painstaking comparisons and a scientific study led to the present attribution. The assertion that the bust represents Fracastoro was made to the museum authorities by the dealer in antiquities, a Roman, Giacomini by name, who also stated that he had bought it as such in Verona. There is no inscription or other document to strengthen this tradition.

In comparing the features of this bust with any of the others of Fracastoro, one is immediately struck by some obvious differences, so much so that one is inclined to dismiss any

consideration of their representing the same person. We have always seen Fracastoro with a beard. On the bronze head we see only the rough, unshaven chin and upper lip, the head cropped, not shaved; and as we examine the features, involuntarily we recall the Hippocratic facies: "a sharp nose, hollow eyes, collapsed temples; the ears cold, contracted and their lobes turned out; the skin about the forehead rough, distended and parched . . ." The majesty of death hovers over this face, striking and repellent. Could it perhaps be that the artist has made a death mask from the dead Fracastoro, worked it over slightly in certain parts, the eyes, for instance, adding the bust portions to it, as a preliminary study for the statue which the Senate had ordered of him? It is obvious that these questions cannot be answered positively, but we do know that such a procedure was not uncommon among the artists of that time, who strove for most realistic representation. From this very striving came, in great measure, the impetus which anatomy received in those days. Of Verrocchio, for instance, we know that he used plaster casts of any part of the human body for models in his work, and masks from the living as well as from the dead were still more frequently employed in this way. An exact comparison of the head of this bust with that of the statue alone might decide what there is to this conjecture. It is natural that Cataneo would have tried to remove in the statue the characteristic features of the death mask and add, of course, the beard, which may have been clipped off for the taking of the mask. Probably while making such modifications the artist would have preserved the general proportions, especially those of the bony parts of skull and face. An exact comparison may be possible, although several attempts to obtain good pictures of the head of the statue have so far failed on account of its elevated and inaccessible position. Until such a comparison decides the question one way or the other, we may safely assume that the bronze bust represents Fracastoro at a more advanced age than the other portraits. He was seventy years old when he died in 1553, while, as we have seen, he appears as a vigorous man of about fifty in the most authentic representation we possess.

This bronze bust being one of the best examples of Cinquecento sculpture in Vienna, the museum authorities are naturally interested to know whether or not it represents Fracastoro.

In my studies on the subject I have been aided by them in various ways, and my particular thanks are due to Professor Hermann, the learned custodian of the Hofmuseum, as well as to the directors of the civic museums in Padua and Verona, Professor Moschetti and Professor Rizzoli.

This iconographic problem will retain its interest to medical men, no matter what the result of further research may be. This is the only excuse I can offer for presenting my study in an unfinished stage.

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# AN EXPERIMENTAL STUDY OF THE FACTORS RESPONSIBLE FOR NON-INFECTIOUS BONE ATROPHY.\*

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## INTRODUCTION.

The purpose of this investigation has been to secure more information of an experimental nature concerning the causes of bone atrophy. The atrophic changes which accompany infectious processes have not been considered here.

The clinical importance of this condition has been recognized for some years, but it is only recently that active measures to combat it have been advocated in the treatment of joint injuries, fractures, etc. Lovett<sup>14</sup> has drawn attention to a series of interesting—occasionally incapacitating—complications, such as varying degrees of ankylosis, articular swelling, pain and increased susceptibility to fatigue which may follow the presence of such an atrophy. He emphasizes the necessity of considering these possible after-results in treating all orthopedic cases, and of instituting appropriate therapy when immobilization plays a prominent part. The occasional occurrence of spontaneous fractures in patients showing an advanced atrophy of the bones emphasizes still more the possible consequences of this condition.

While it appears that the therapeutic test has demonstrated the efficacy of active and passive motion, massage, etc., in combating bone atrophy, we shall not be in a position to use these measures to their best advantage until more is known concerning the factors which are directly responsible for such a complication. Various hypotheses have been advanced from time to time, the oldest perhaps being that such changes are due to the influence of the central or the peripheral nervous system. In this way the descriptive terms "trophic atrophy" and "nervous reflex atrophy" arose. Later an important rôle was ascribed to inactivity. More recently emphasis has been laid upon the nutrition of the part involved, a change in the vascular supply being recognized as the principal factor responsible for immobilization or disuse atrophy.

The series of experiments reported here were undertaken in order to ascertain more definitely, if possible, the relative importance of these several hypotheses.

## METHODS EMPLOYED.

The experiments were conducted on thirty-eight rabbits and nine dogs. In both series of animals the bones entering into the formation of the ankle and wrist joints proved to be the most suitable for such a study. Structural changes in the

cortex and medulla were followed by means of the Roentgen-rays. The limb opposite the one experimented upon was used as a control. As frequent X-ray examinations were made in each case, it was possible to follow closely the appearance and the progress of atrophic changes.

Where nerves were cut, it was found that wrapping the affected limbs in adhesive plaster protected the skin from superficial and deeper infections. Infected animals were discarded from the series. Throughout the operative procedures the rabbits and dogs were kept thoroughly anesthetized with ether.

The results from the experimental work are discussed under four principal headings: (1) the nervous influences in bone atrophy; (2) the blood supply in atrophy; (3) inactivity or immobilization in atrophy; (4) immobilization in bone repair. Summaries of the more typical protocols have been included in each of these divisions.

## NERVOUS INFLUENCES IN BONE ATROPHY.

EXPERIMENT I.—*Dog No. 4. Laminectomy.*—Resection of a centimeter of the posterior or sensory roots of the lower three lumbar and first sacral spinal nerves, left side. Healing *per primam*. During the first few days of convalescence the left hindfoot appeared weaker than the right. While running, the leg was held above the ground; while walking, loss of sense of position was apparent. On the ninth day the gait appeared practically normal; the animal ran and jumped as freely as before operation. The dog was given ample exercise each day.

Roentgen-ray examinations made at frequent intervals revealed no structural differences in the bones of the two hindlegs, even as late as two and one-half months after the root resections.

EXP. II.—*Dog No. 2. Laminectomy.*—Resection of a centimeter of the anterior motor roots of the last three lumbar and the first sacral spinal nerves, left side. Healing *per primam*. The dog was active on the day following the operation. In walking, running, defecating etc., there was a complete disability of the involved leg. The animal received ample, active exercise each day.

At the end of the fourth week the Roentgen-ray examination showed very slight structural differences between the bones of the hindlegs. Two weeks later (six weeks in all) there were definite signs of beginning atrophy indicated by the disappearance of some of the finer trabecular lines and the presence of small areas of absorption in the cortices of the tibia and fibula. Two months after the operation there was a further advance in the atrophic process—a thinning of the cortical portions of the metatarsal bones. Some slight additional changes were apparent at the expiration of two and one-half months.

EXP. III.—*Dog 5.*—A plaster cast was applied to the left foreleg so as to immobilize it completely. The dog was unable to step on the limb and made no attempts to use the shoulder muscles of this side.

\* From the Roentgenological Department of the Peter Bent Brigham Hospital and the Laboratory of Surgical Research, Harvard Medical School, Boston.



Structural changes appeared about the fourth week. They were found to advance somewhat more rapidly in this animal than in that of the preceding experiment (Exp. II). About two months after the application of the cast, signs of a moderately advanced atrophy were seen both in the cortex and in the medulla of the bones of the foreleg.

EXP. IV.—*Rabbit No. 13.*—About a centimeter of the left sciatic nerve was excised high in the thigh. The animal was kept in a cage with other rabbits and was active throughout the period of observation. Healing *per primam*.

No difference in the two legs was noticed during the following four weeks. One and one-half months after the operation slight changes were visible: the cortex appeared a little thinned and the trabeculae, though distinct, were somewhat finer. After two additional weeks the medulla was less dense, and the shadows cast by the bones as a whole were slightly less clear.

EXP. V.—*Rabbit No. 19.*—Small segments of the left anterior crural and the sciatic nerves were excised high in the thigh. Healing *per primam*. Active exercise.

Roentgen-ray examinations showed a beginning atrophy at the end of the second week—the cortex a trifle less compact and structural lines in the medulla somewhat fainter. There was even a possible difference seven or eight days after the operation. Subsequently a slow advance in these changes was noted. A comparison of the roentgenograms made at corresponding intervals after operation from this experiment with those from Exp. VIII showed more atrophy in the latter.

*Discussion.*—The conception that atrophy of bone is controlled to a greater or lesser extent by nervous influences has occupied men's minds as long as the subject of atrophy has formed a problem for speculation. We find in Petit's <sup>18</sup> *Traité des Maladies des Os* that atrophy is an accident which supervenes not at the beginning, but later, from enfeeblement of nerves and arteries which continue to be compressed, either by exuberant callus or by too tight bandaging.

Schiff,<sup>22</sup> in 1854, cut the sciatic and crural nerves in young dogs and observed first an atrophy and later (12-18 months) a hypertrophy of the bones (*entzündliche Knochenneubildung*). Nasse<sup>17</sup> and Mantegazza<sup>15</sup> repeated these experiments and rejected all animals showing infections. On the paralyzed side they found a general atrophy of all of the constituents of the limb. This was interpreted as being trophic in origin.

Rasumovsky,<sup>20</sup> from an experimental study in 1884, ascribed a considerable rôle to trophic nerves which, he believed, influenced the circulation of the part. A few years later Wolff<sup>27</sup> expressed much the same view. Schuchardt<sup>23</sup> also emphasized the neurotrophic factor as the most important in the development of bone atrophy. Sudeck<sup>25</sup> accepts Nasse's conclusions and cites cases of atrophy due to peripheral nerve injuries. Sudeck, Kienböck<sup>12</sup> and Exner<sup>6</sup> regard the rapidly appearing forms of atrophy as reflex or trophoneurotic in origin.

Recently Brandes<sup>4</sup> has shown that atrophy may arise from inactivity much sooner than was formerly believed. He considers that the rapidly appearing atrophies are caused by inactivity and not by neurotrophic or reflex influences.

The effect of dividing the posterior or sensory nerves which supply the leg and foot is shown by Experiment I to be minimal. No signs of atrophy were evident in this case as late as two and one-half months after the operation. As the anterior or motor roots were left intact, complications arising from inactivity were obviated.

Experiments IV and V illustrate the effects of destruction of peripheral nerves. A moderate degree of atrophy was observed in both. This probably was an inactivity atrophy due to the paralysis of the muscles. On comparing the degree noted in each of these experiments with that observed in Experiments X and XI, it was found that the changes were more advanced in the latter. As frequent observations of the animals showed that a greater immobilization was produced by the casts than by cutting the nerves, the conclusion is justifiable that the atrophy present in Experiments IV and V was due to inactivity alone. It is thus apparent that peripheral nerves have no direct influence on the production of bone atrophy.

The purpose of Experiment II was to determine whether motor nerves exert any direct trophic influences upon the nutrition of bone. A certain amount of atrophy was noted subsequent to the motor-root resections, but since a comparison of the plates from this experiment with those from Experiment III reveals more advanced changes in the latter, this atrophy may fairly be attributed to inactivity. The dog with the motor root divisions gave the affected limb considerable passive motion; whereas the one with a leg immobilized in plaster held the corresponding shoulder muscles firmly fixed.

In all of the published work which concerns the nervous influences in bone absorption no satisfactory means have been employed to differentiate between the trophic and the disuse factors. Up to Brandes' investigations, moreover, there has been a failure to recognize the early changes which result from inactivity alone. These facts together with the negative nature of the results from the nerve experiments reported here, accordingly, warrant the conclusion that the sensory and the motor nerves of the limbs exert no direct reflex or neurotrophic influences on the development of bone atrophy.

#### THE BLOOD SUPPLY IN BONE ATROPHY.

EXP. VI.—*Dog No. 3.*—Ligation and division of the right subclavian vein. Healing *per primam*. On the day following the operation a slight puffiness was evident in the affected paw. The dog was nevertheless active, walking and running about the yard as usual.

Roentgen-ray examinations made over a period of two months revealed no structural changes in the bones of the operated leg.

EXP. VII.—*Rabbit No. 5.*—Ligation and division of the femoral and saphenous veins, left hindleg. Healing *per primam*. For a day or two there was a slight fullness of the affected forelimb. The animal used all four legs actively throughout the period of observation.

Roentgen-ray examinations, made at frequent intervals for two and one-half months, showed no changes indicative of atrophy in the operated leg.

EXP. VIII-A.—*Dog No. 6.*—Ligation and division of the ulnar and common interosseous arteries in the right foreleg. Healing *per primam*. The dog was active on all four limbs throughout the weeks of study.

Roentgenograms made at the end of the first week showed no differences in structure between the bones of the two forelegs. Seven days later there were still no definite indications of a beginning atrophy.

EXP. VIII-B.—(Two weeks subsequent to part A.) Ligation and division of the radial artery near its point of origin in same leg (right foreleg). Healing *per primam*. During the following seven or eight days the surface temperature of the affected paw remained



considerably lower than that on the control side. Nevertheless, at the end of this time no appreciable structural differences were found between the bones of the two forelegs. Roentgenograms made at later dates also showed absence of any clearly defined atrophy. It should be mentioned that in this half of the experiment the dog was again given ample exercise each day.

EXP. IX.—*Rabbit No. 4.*—Ligation and division of the right femoral artery high in the groin. Healing *per primam*. The animal continued active subsequent to the operation.

No structural changes were noted up to the sixth week. At this time the shadows cast by the ankle-bones appeared to be slightly less distinct on the affected side. No definite atrophy was noted, however, in either the cortex or the medulla two months after the operation.

*Discussion.*—Helferich<sup>10</sup> and Schüller<sup>24</sup> have each reported experiments in which they observed an increased bone growth following the establishment of an artificial venous hyperemia. Wichmann<sup>26</sup> and Stoltzner, on the other hand, found an atrophy, occasionally marked, in fractured thigh-bones which were suspended vertically for a considerable time. This they attributed to an arterial and venous anæmia resulting from the elevated position of the limbs.

By means of a thermometer Berginen<sup>2</sup> demonstrated differences between the affected and the normal thighs in numerous cases of hip disease. The atrophy present in these patients he ascribed to an impairment of the nutrition of the parts.

Marked atrophy without immobilization in a class of patients with joint disease Legg<sup>13</sup> believes is due to an interference with the blood supply from pressure on the femoral artery. He considers that the atrophy which results from disuse or functional inactivity is due to changes in the nutrition of the part through vasomotor influences.

In Experiments VI and VII there was sufficient interference with the circulation to cause a transitory edema of the forelegs. As no subsequent changes in the structure of the bones were noted, it appears probable that passive hyperemia in itself brings about very little, if any, atrophic changes. It is to be noted that the complication of inactivity did not enter into these experiments, since the animals had ample exercise each day and used the operated as well as the control foot.

Experiments VIII and IX were carried out in order to ascertain more satisfactorily the significance of disturbances in the arterial blood supply. As the animals were active, using all four feet throughout the periods of Roentgen-ray observation, the bones in the operated limbs were subjected to vascular changes of an anæmic type without being in any way immobilized. The difference in surface temperature noted in Experiment VIII affords evidence that the operations were successful in establishing an anæmia of the affected part. Clinical cases with well-defined disuse atrophy, as a rule, show no such signs of nutritional disturbances. The fact that no definite atrophic changes were discernible in either of these experiments suggests that the atrophy resulting from inactivity is due rather to a diminution or loss of the functional stimulus normal to bone than to vascular changes—*i. e.*, a local anæmia. Should the anæmia be sufficiently marked to seriously affect the viability of the part, an ischemic atrophy of all the tissues would result. The atrophies noted by Legg in patients showing no immobili-

zation may be explained in this manner, though the bacterial toxins present in many cases of hip disease are undoubtedly responsible for some degree of absorption.

Concerning the part played by vasomotor nerves in the blood supply of the limbs, there is still considerable uncertainty. While various physiologists have shown that muscular activity is accompanied by an increase in the blood flow through the muscle, there is still no agreement as to the significance of either vasodilator fibers (Goltz)<sup>8</sup> or of the chemical action of metabolic products, such as lactic acid, etc. (Bayliss)<sup>1</sup>. At present, according to Howell,<sup>11</sup> we may accept the view advocated by Gaskell<sup>7</sup>. The latter holds that the vasomotor supply to the muscles consists essentially of dilator fibers. Whenever the muscles contract these are brought into action, providing a blood supply proportional to the functional activity of the part.

In the absence of further evidence we may accept the same explanation for the regulation of the nutrition of bone. From this, however, it does not necessarily follow that the atrophic changes which muscle and bone undergo when they are immobilized result entirely or in a large measure from the decrease in the local supply of nourishment which accompanies such states of inactivity. A normal limb, if kept at rest, will continue to receive a quantity of blood perfectly adequate for such a physiological state.

In functional hypertrophy the opposite relations probably exist. The parts enlarge, grow, not as a result of an augmented blood supply, but due to the increased demands made upon them. They respond to the additional functional stimuli. The greater vascularity simply keeps pace with the growth, supplying the increased requirements for nourishment.

Since the nerve fibers regulating the vasomotor tone of the extremities must enter the limbs by way of the brachial and lumbar plexuses, Experiments IV and V afford examples of limbs isolated from reflex vasomotor control. In Experiment I, on the other hand, such fibers as may have entered the plexus through the post-ganglionic communications remained intact (see below). Notwithstanding this loss of central control the bones in the affected parts showed no atrophic changes attributable to vasomotor influences.

From the experimental work of Goltz<sup>8</sup> it appears that when the spinal cord is destroyed except in the cervical region there is a paralysis of vascular tone in the posterior extremities. Since this tone may ultimately be restored, the resumption of tonicity must be referred either to the properties of the muscular coats of the arteries themselves, or to the activity of the sympathetic nerve cells that give rise to the post-ganglionic fibers. If we were to assume that the absence of atrophy in the animals cited is due to such a resumption of vascular tone—*i. e.*, to a readjustment of the altered circulation—Experiments IV and V would indicate that this probably results from the activity of the muscular coats of the arteries themselves, for the post-ganglionic fibers were severed in the divisions of the sciatic and anterior crural nerves.

While it is conceivable that a re-establishment of the vascular equilibrium may take place through the activity of the arteries themselves, it appears unlikely that the changes in nutrition,



which such a resumption of vascular tone is capable of effecting, are sufficiently marked to account for the absence of bone atrophy in these animals. This view is borne out by the results from Experiments VIII and IX. In the latter experiments a very definite local anæmia was produced; nevertheless, no atrophic changes were noted in the parts affected.

#### INACTIVITY IN BONE ATROPHY.

EXP. X.—*Rabbit No. 6.*—Plaster cast applied to right hindleg so as to immobilize the joints in the usual sitting posture.

Roentgenograms made on the fourth day of fixation showed that the trabecula within the calcaneus of the affected limb were less distinct than on the control side. All of the finer lines were visible, however. At the end of the first week these changes had advanced so that there was a rarefaction of the distal ends of the tibia, calcaneus and the other tarsal bones. This was marked in the posterior end of the calcaneus. The outlines of the cortex were hazy. The crest of the tibia was indistinct, especially near the internal malleolus. Two weeks following the immobilization the cortices of the distal end of the tibia and of the tarsal bones were definitely thinned. The shadows cast by the trabeculae now appeared more indistinct and delicate. At the end of two months the structural changes were marked. Near the epiphyseal line at the lower end of the tibia the usual markings were largely absent. There was rarefaction, especially advanced in the posterior portion of the calcaneus, and fewer lines were present in the medulla. The cortices of even the metatarsal bones were now greatly thinned. A comparison of the roentgenograms (made at corresponding intervals after operation) from this experiment with those from Exps. IV and V, shows a more advanced atrophy in the former.

EXP. XI.—*Rabbit No. 28.*—A plaster cast was applied to the right hindleg—fixed in the completely extended position. The arrangement embarrassed the animal in walking about its cage and afforded a very effective fixation of the part.

Changes in the finer architecture and in bone density appeared about the fourth day, as in Exp. X. In later examinations, however, the atrophy was found to advance somewhat more rapidly in the former.

EXP. XII.—*Rabbit No. 26.*—Tendo achillis cut in right hindleg. Healing *per primam*. The animal was active on its three normal feet on the following day.

One week later roentgenograms showed definite atrophic changes. A rarefaction of the distal end of the tibia and of the tarsal bones was visible, particularly in the posterior end of the calcaneus. The outlines appeared softened and the trabeculae somewhat indistinct. The cortex of the tibia near its anterior margin was especially hazy. Two weeks more disclosed a thinning of the cortices of the lower tibia and the tarsus and a loss of numerous trabeculae within the bones. The remaining medullary shadows were more delicate than formerly. As compared with the changes noted in Exp. X at the expiration of two weeks the findings here showed more structural modifications (thinning of the cortex and loss of the trabeculae) but less general rarefaction (decrease in the intensity of the shadows cast by the bones). During the subsequent four months there were signs of a progressively increasing atrophy. The last roentgenograms showed a rather striking difference between the two sides: the cortices of the tarsus and metatarsus were much thinned, the finer structural lines were very faint or absent especially in the calcaneus, and the bones, as a whole, appeared much rarefied.

EXP. XIII.—*Rabbit No. 11.*—Tendo achillis cut in right hindleg. Posterior tibial artery ligated and divided high in the calf. Healing *per primam*.

Subsequent roentgenogram studies showed changes corresponding to those noted in the previous experiment (Exp. XII). The division of the artery apparently did not hasten the atrophic process.

EXP. XIV.—*Rabbit No. 20.*—Small segment of sciatic nerve resected high in the right thigh. Right hindleg immobilized in plaster. Healing *per primam*.

Two weeks later practically the same changes were found here as were noted in Exp. X. In roentgenograms taken subsequent to this period, the progression of the atrophy corresponded very closely to that observed in the latter experiment.

*Discussion.*—The fact that inactivity may lead to atrophic changes in the affected bones has been recognized for many years. During this period, however, there has been a great difference of opinion concerning the relative importance of inactivity as compared with neurotrophic influences and vascular changes.

The conclusion drawn by Brackett<sup>3</sup> from a clinical study was that functional inactivity may alone account for the atrophy seen in joint disease.

Sudeck,<sup>25</sup> Kienböck<sup>12</sup> and Exner,<sup>6</sup> while recognizing a true disuse atrophy, taught that it is of very slow onset. In rare instances Sudeck found changes as early as six to eight weeks following a fracture.

The recent investigations of Brandes<sup>4</sup> have afforded a new conception of the part played by immobilization. Even where the loss of function in a part is only partial, an inactivity atrophy may soon appear. The greater the inactivity, moreover, the more intense are the atrophic changes.

These observations are consistent with the histological findings of Roux,<sup>21</sup> who showed that not only do certain trabeculae of the medulla atrophy or disappear when trauma or a change of function establishes a new adjustment of the lines of force in the bone, but that a compensatory hypertrophy may occur in trabeculae, and new ones may even appear. In other words, he found a very striking physiological adaptation of the structure of a bone to its function.

The results from Experiments X, XI and XII confirm the findings of Brandes. The amount of atrophy was found to be proportional to the degree of fixation secured for the part. Rarefaction and a loss of the finer structural detail, furthermore, were observed at a very early date. Brandes reports changes at the end of eight days in cases in which the Achillis tendon had been cut. In the experiments cited here the earliest changes were noted on the fourth day after immobilization.

The combination of fixation and slight local anæmia, as planned in Experiment XIII, seemed to exert no accelerating influence on the process of bone absorption. Nor was any increase in the rate of the changes found, when to the immobilization in plaster was added a transection of the nerve supplying the foreleg—Experiment XIV. The fixation secured by the cast probably exceeded that which resulted from the nerve division; the hip muscles certainly were more active in the latter. When clinical cases exhibiting atrophy of a non-infectious type are analyzed and the confusing conception of trophic influences dispelled, the inactivity element is found to play a very prominent part. Atrophies of this type are frequently overlooked, as Sudeck, Brandes and others have pointed out.

The fact that fixation leads to atrophic changes in the immobilized limb indicates the importance of functional activity in the normal nutrition of bone. While numerous writers



explain this atrophy by the fact that organs in general receive less blood supply when they are kept at rest, it was pointed out in an earlier paragraph that there is much evidence against such a view. Certain experiences in bone transplantation, furthermore, suggest that the blood supply is only one of the factors responsible for the survival of the graft. Murphy,<sup>16</sup> Phemister,<sup>19</sup> Davis and Hunnicutt<sup>5</sup> and others have shown that when bone is transplanted into soft parts—muscle, fat, etc.—little or no proliferation occurs and the graft is gradually absorbed. The opportunities for establishing a new blood supply in muscle, of course, are excellent. It seems improbable that such a transplant ultimately perishes through want of the proper nourishment. What does appear likely is that bone transplanted into such an environment atrophies and disappears, because it has ceased to receive the functional stimuli normal to osseous tissue in general.

A somewhat similar factor appears to be necessary for the activity and growth of certain more highly specialized tissues. In transplanting pieces of thyroid Halsted<sup>9</sup> has pointed out that the grafts will take only when there is a deficit of thyroid tissue in the body. This may be interpreted to mean that the transplants require a functional stimulus to survive.

#### IMMOBILIZATION AND BONE REPAIR.

EXP. XV.—*Dog No. 7.*—A hole from 4 to 5 mm. in diameter was drilled through each radius in an antero-posterior direction. Care was taken not to injure any nerves or vessels and to make the steps of the operation similar on the two sides. The right foreleg was then immobilized in plaster to prevent the dog from using it in standing, walking, etc. The opposite limb was left unbandaged. Healing *per primam*.

A Roentgen-ray examination on the following day showed a clear cut, circular defect in each radius. It was likewise noted that the cortex and medulla of each bone in the foreleg on either side cast corresponding shadows. Two weeks later the dark spot made by the defect in the right tibia showed no appreciable change; that in the left leg, however, was slightly cloudy indicating a more active process of repair on this side. Subsequent examinations showed a considerably slower progress in healing on the immobilized side. Slight structural changes in the tibia and fibula pointing to an inactivity atrophy were noted about the fourth week. This process advanced slowly throughout the experiment.

*Discussion.*—Since immobilization plays an important rôle in the development of atrophy, it is fair to suppose that it likewise influences the rate of repair in fractures and other bone injuries—presumably by delaying the formation of callus. Some have assumed that absolute rest is essential to the repair of bone, just as it is favorable to the healing of wounds elsewhere in the body. Others, however, while recognizing the necessity for the maintenance of a proper alignment of the fragments, have held that perfect fixation in itself is unfavorable to the most rapid healing.

In order to obtain more light on this problem Experiment XV was carried out. Since actual fracture of the tibiae would have entailed the use of splints on either foot it was found advisable to make use of the expedient described above whereby exactly similar amounts of repair were called for in the two limbs.

The delayed healing on the immobilized side suggests that

the factors which are directly responsible for the changes characteristic of simple disuse atrophy are also active when a part is fixed in splints or plaster in treatment for fractures. This may explain in a measure the sluggishness of healing noted in certain cases of fracture, for it is well known that the degree of inactivity atrophy may be greater in one subject than in another, subsequently to the same period of immobilization.

#### CONCLUSIONS.

I. A destruction of the sensory nerves to a part occasions no direct local atrophy of bone. A destruction of the motor nerves, on the other hand, leads to a certain amount of atrophy. This, however, is indirectly the result of inactivity or disuse and is directly proportional in extent to the degree of paralysis present in the part.

II. Local venous congestion leads directly to no recognizable changes in the structure of bone. Local anæmia due to injury to the arterial supply, except in an extreme degree, likewise occasions no bone atrophy so long as the part remains functionally active.

III. Inactivity atrophy may appear very soon after immobilization of a limb—as early as the fourth or fifth day in rabbits. It is probably due to a decrease or to an absence of the functional stimuli necessary to the normal nutrition of bone.

IV. Immobilization retards the process of repair in bone injuries.

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## NOTE ON THE ORIGIN OF THE LACTIC ACID BACTERIA IN MILK

By PATRICK F. MCGUIRE.

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It has recently been shown by Shippen<sup>1</sup> that the principal organism concerned in the normal souring of milk in Baltimore is the species known usually as *Streptococcus lacticus*, for which, however, the term *Bacterium g ntherii*, Lehmann and Neumann, he regards as the correct designation. This species occurred in nearly all the samples of milk examined by Shippen, and in the majority of instances was the predominant one.

In view of Shippen's findings it becomes a matter of interest to determine the ultimate source of this species in nature. Three different possible places have been suggested from which the organism could find a ready entrance into milk. It has been suggested: (1) that the species is a normal inhabitant of the cow's udder, in which event it would, in all probability, always be present in milk; (2) that the species is a regular constituent of the cow's saliva, in which event it would find its way into milk from the cow's udder whenever the animal was not prevented from licking the udder with her tongue; finally (3) that the organism is a constituent of the dung, and consequently would always appear in the milk when proper precautions were not carried out to prevent the contamination of the milk by faecal material. The present inquiry relates only to the third of these hypotheses, namely, the question of the presence of *Streptococcus lacticus* in cow dung and its relative frequency there.

Two different methods were employed for the isolation of this organism. In the first method plates of litmus-dextrose-agar were poured directly from the dejecta, incubated 24-48 hours, and the small, fine colonies thought to be *Streptococcus lacticus* picked up, transferred to agar, subcultured and identified. The essential points necessary for the identification of this species, as indicated by Shippen, were kept clearly in mind and only those organisms exhibiting these cardinal features were regarded as *Bact. g ntherii*. In the second method, a series of litmus-milk tubes was inoculated with small particles from the dejecta with the expectation that this species would show an especial predilection for milk, developing there to the exclusion of other organisms. From these milk tubes showing the characteristic acidification and coagulation, plates were now poured on litmus-dextrose-agar and the typical colonies fished. By the use of both methods it was shown that the lactic acid organisms are constantly present in cow-dung. In 7 consecutive samples they were isolated in each case and by both methods. They were, however, by no means abundant and did not constitute the main predominating species.

The attempt was now made to gain some approximate idea as to the numerical ratio that these organisms bear to the other

bacteria in the bovine dejecta. To determine this point 1 cc. of the dejecta was suspended in 100 cc. of sterile water from which dilutions were made and quantities of the emulsion varying from 0.1 to 0.0001 cc. plated in litmus-dextrose-agar. It was found that the plates poured from the 0.01 cc. dilution were fairly thickly seeded and yet contained many isolated colonies. One hundred colonies from the 0.01 cc. plate were now fished, transferred to agar, subcultured and identified. The percentage of the various organisms in each sample was thus roughly obtained. The relative numbers of *Streptococcus lacticus* varied from 4 to 12 per cent, as can be seen in the following table. In but one instance (sample 6) was the organism lacking from the plates.

Samples.	Organisms.	Percentage of Occurrence.
1.	Coli-aerogenes group .....	96
	<i>Streptococcus lacticus</i> .....	4
2.	Coli-aerogenes group .....	85
	Yellow staphylococcus .....	4
	<i>Streptococcus lacticus</i> .....	12
3.	Coli-aerogenes group .....	88
	<i>Bacillus subtilis</i> .....	4
	<i>Bacillus megatherium</i> .....	4
	<i>Streptococcus lactifcus</i> .....	4
4.	Coli-aerogenes group .....	72
	White staphylococcus .....	8
	<i>Bacillus megatherium</i> .....	4
	<i>Bacillus petasites</i> .....	4
	<i>Bacillus mesentericus fuscus</i> .....	4
	<i>Streptococcus lacticus</i> .....	8
5.	Coli-aerogenes group .....	80
	Unidentified bacilli .....	12
	<i>Streptococcus lacticus</i> .....	8
6.	Coli-aerogenes group .....	12
	Unidentified bacilli .....	84
	<i>Bacillus megatherium</i> .....	4
7.	Coli-aerogenes group .....	72
	<i>Bacillus subtilis</i> .....	8
	Yellow staphylococcus .....	4
	Unidentified bacilli .....	8
	<i>Streptococcus lacticus</i> .....	8

## CONCLUSION.

As previously shown by Esten,<sup>2</sup> the lactic acid organism known usually as *Streptococcus lacticus* is a normal constituent of cow dung. While its presence in other regions in the animal has been indicated by others, in view of these findings the possibility must be borne in mind that the lactic acid organisms in milk have one constant source of origin in the dejecta of the animal.

<sup>1</sup> Shippen: Principal Types of Organisms in Baltimore Milk. The Johns Hosp. Bull., April, 1914, XXV, No. 278.

<sup>2</sup> Esten: *Bacterium lactis acidii* and its sources. Bulletin No 59, Starr's Agricultural Experiment Station, August, 1909.



## NOTES ON NEW BOOKS.

*Obstetrical Nursing.* By CHARLES SUMNER BACON, Ph. D., M. D.  
Cloth, \$2.00. (Philadelphia: Lea & Febiger, 1915.)

This is an exceedingly helpful reference book on obstetrics—far above the average in regard to practical advice, and with some very sensible ethical notes.

The care of the patient during pregnancy and the puerperium is fully and clearly considered, as well as the complications that might arise and the treatment expected of the nurse in each instance.

While the author realizes, as he remarks in the preface, that the nurse should have a comprehensive knowledge of the scientific side, he does not take up the pelvic anatomy, ovum, or mechanism of labor, clearly or fully enough to make the book of value as a text-book. He also devotes very little time to the disturbances of metabolism as compared with his consideration of the other derangements and abnormalities of pregnancy.

The book would be a helpful addition to a nurse's library.

E. A. T.

*Students' Manual of Gynecology.* By JOHN OSBORN POLAK, M. S. C., M. D., F. A. C. S. (Philadelphia and New York: Lea & Febiger, 1915.)

An attempt to reduce any subject to manual form is always a difficult task and usually results in an incomplete volume. Dr. Polak's work is no exception. The subject-matter is well arranged, but the descriptions are very brief and not infrequently important conditions are dismissed with a single statement. The illustrations are numerous but very diagrammatic.

J. C. N.

*The Tenth and Eleventh Reports of the Henry Phipps Institute, of Philadelphia, 1915.* Published by the Henry Phipps Institute, Philadelphia.

These reports are of great interest. The Tenth contains an article on Pulmonary Acoustic Phenomena by C. M. Montgomery, M. D., of the Henry Phipps Institute, and E. A. Eckhardt, Ph. D., of the Department of Physics, University of Pennsylvania. The study has been dealt with under two main headings, namely, "The Voice Sounds, Spoken and Whispered," and "The Respiratory or Breath Sounds," and a summary completes this excellent article. Seldom has this subject been treated more fully or carefully, and it should be of the greatest value and help not only to the student and general practitioner, but also to the physician who is specializing in diseases of the lungs, especially if he is teaching students.

The Eleventh Report deals with the "Study of the Housing and Social Conditions in Selected Districts of Philadelphia," by Frank A. Craig, M. D., Instructor in Medicine. Two questions are considered, namely, "Housing" and "Living Conditions." Under the head of "Housing" are included "Grading of Houses According to the Special Classification," "Housing in Detail," "Summary of Housing" and "Importance of Good Housing and Its Relation to the Health of the Public."

"Living Conditions" are considered from the standpoint of "Social Status of Families Studied," "Crowding," "Rent," and "Nationality." The author has been impressed by the inadequate measures adopted to protect the public against disease. He feels that the analogy between crime and disease is a very close one, and that education of the public is essential, there being one large portion of the population for whom education alone is sufficient to prevent them from performing acts prejudicial to the public welfare, but that the remainder are prevented from such acts only by police supervision. Hence he holds that the problem of the health of the public will never be solved until a vigorous,

widespread campaign of education has reached the first, and sanitary police, or inspectors with police powers, are provided for the second group. The article contains numerous valuable charts and an instructive map of the part of the city studied. The report is well presented and should prove very valuable.

K. H. V.

*Therapeutics of the Circulation.* By SIR LAUDER BRUNTON, M. D., F. R. S., F. R. C. P. Second edition, \$2.50 net. (New York: Paul B. Hoeber, 1914.)

In 1908 Sir Lauder Brunton published a series of eight lectures that he had delivered three years before in the Physiological Laboratory of the University of London. They were presented in accordance with the general purpose of the University to have recent investigators describe their own researches. These particular lectures were very generally devoted to physiology and pharmacology, and were abundantly illustrated from the author's rich experience in experimental investigation. No effort was made to discuss problems other than those which had occupied the especial attention of Sir Lauder. The results, therefore, did not develop a text-book, but constituted individual chapters in the domain of experimental physiology, with interesting remarks on practical therapeutics that followed therefrom.

In 1914 a completely revised edition was published which, however, is based on the preceding volume. There is still an immense amount of interesting physiological facts concerning the organs of circulation, with an absence of any system in the developing of such studies. Therapeutics becomes a very prominent feature, but is distinctly subordinate, as it should be, to physiology, which supplies the reasons for many therapeutic procedures. The drugs discussed belong rather to the past generation in the large number and complex combinations employed; but, withal, they are distinctly regarded as adjuvants to the fundamental methods of treatment—rest, nutrition, and elimination.

The physiology and pharmacology contained in the book makes it instructive and valuable—a storehouse of concise reasoning and adequate explanation in the science of the physiology of the vascular system. The book, while not so systematic and while partially devoted to therapeutics, is comparable to Krehl's *Pathological Physiology* in its effort to develop a fundamental understanding of cardiac knowledge and investigation.

*Therapeutics of the Circulation* is published in a small pocket-sized volume of five hundred pages, with fair type, an abundant index, and an excellent bibliography. While not a text-book nor a satisfactory reference volume, it is an example of "summer reading" that could be perused equally advantageously by the second-year student or the active practitioner, who would gain an understanding of many physiological discussions, and especially a comprehension of a rational therapeutics in so far as therapeutics has a physiological basis.

E. W. B.

*Osler's Modern Medicine.* Vol. V. Diseases of the Nervous System; Diseases of the Locomotor System. \$5.00 net. (Philadelphia: Lea & Febiger, 1915.)

This volume comprises practically the same subjects as Vol. VII in the first edition, and shows with the preceding volumes of the second edition the improvements in format, letter press and illustrations. The articles are by men whose names are familiar to the English speaking world, and reach a very high average of excellence. Especially noteworthy are Barker's introduction, Cushing on tumors of the brain and meninges, Thomas on diseases of the cerebral blood-vessels, and Spiller on the motor tract.

The second division includes myositis and Thomsen's disease



by Steiner, arthritis deformans by McCrae, which is transposed from the motor and trophic group of the first edition, osteomalacia by Dock, and the rarer dystrophies and plastic disturbances of the bones by Emerson.

The general index covers 63 pages and is very well arranged. The second edition, as a whole, is much more attractive than the first, and while it lacks some of the references and historical material of the original issue, it will prove the most generally acceptable system in English.

T. R. B.

*International Clinics.* Vol. III. Twenty-fourth Series. Edited by HENRY W. CATTELL, M. D., and associates. Cloth, \$2.00. (Philadelphia and London: J. B. Lippincott Company, 1914.)

This volume contains 26 papers on a variety of medical and surgical subjects. Worthy of mention are the articles by Deaderick on malaria carriers; by Pemberton, on the treatment of rheumatic arthritis; and by Hess, on the use of vaccines in pertussis. The leading article is devoted to the surgical practice of John B. Deaver, of Philadelphia, covering briefly the operative treatment of about 120 selected cases from his clinic.

With the exception of these articles there is little of interest in the volume. The papers on the treatment of pulmonary tuberculosis and of diabetes mellitus are particularly poor and are commendable only because of their brevity.

P. W. C.

*Balneo-Gymnastic Treatment of Chronic Diseases of the Heart.* By PROF. THEODOR SCHOTT, Bad Nauheim. Pages 191; 87 illustrations and charts. Cloth, \$2.50. (Philadelphia: P. Blakiston's Son & Co., 1914.)

This book gives a description of the methods of treatment in use at Bad Nauheim.

The chapters on the general treatment of cardiac disorders contain but little unknown to the average practitioner; while those devoted to balneo-therapy give one the impression that the results quoted are obtained as much from the general routine of a carefully-regulated mode of life with suitable dietary and a complete change of surroundings as from any special virtue in the bath.

Artificial imitation of the waters is discouraged and the directions for the preparation of effervescing baths in the home are of the most general character.

The chapters on gymnastic treatment, however, are excellent, the resistance exercises being well described and illustrated by numerous photographs with descriptive letter-press. For these we owe Prof. Schott a considerable debt of gratitude.

D. S. L.

*Food Products.* By HENRY C. SHERMAN, Ph. D., Professor of Food Chemistry, Columbia University, New York. (The Macmillan Company, 1914.)

Those who wish to be oriented on food legislation, its preparation, composition and nutritive value, cannot do better than to supplement their studies with this book. It summarizes in a very lucid manner much of the far-scattered effort of the law-

makers and scientists. Especial attention has been paid to the very valuable researches and data gathered by the various state agricultural experiment stations and the United States Department of Agriculture. Most of these publications are far too little known and have not had the prominence and general use they deserve. In this book many of them are referred to, and thus a large field of reference is opened to the reader. Some of the food tables given do not differ from those printed hundreds of times before; those, however, dealing with the excess of acid and base-forming elements, with the ash constituents and with the weight of food in 100 caloric portions, form welcome additions to the dietary tables now available. From a medical point of view, practical tables have yet to be compiled. The present book is a distinct aid in this direction even if it does not solve the problem completely.

H. O. M.

*Diabetes Mellitus.* Designed for the Use of Practitioners of Medicine. By NELLIS B. FOSTER, M. D. (Philadelphia and London: J. B. Lippincott Company, 1915.)

The long-continued interest of the author in diabetes and his personal contributions to our knowledge of the disease well qualify him for presenting this little volume for the use of practitioners of medicine.

Few of the commoner diseases met with are more wretchedly handled by the general practitioner than is diabetes, owing to the fact that he fails to grasp the basic metabolic disturbances which lie at the foundation of the disease. He usually feels that his duty to his patient has been discharged when he has prescribed a diet in which the carbohydrates are restricted or cut off and has then ordered a certain amount of gluten bread, made from one of the numerous gluten flours on the market, all of which are notoriously unreliable and practically all of which are rich in starch. Rarely does he think of watching for evidences of diabetic acidosis, which constitutes the most serious complication of the disease.

The author endeavors to give an unbiased critical judgment of the various theories that have been advanced from time to time to explain the cause of diabetes. It is of interest to note that he is strongly opposed to the theory of von Noorden and his school, that most, if not all, cases are dependent upon some disturbance in the co-relationship of the action of the hormones of the various ductless glands.

Chapters are presented on normal metabolism, sources of glucose in the animal body, experimental glycosuria, acidosis, pathogenesis, history, etiology, pathology, symptomatology, renal diabetes, diagnosis and course of the disease, total metabolism in diabetes, treatment, and identification of sugars in the urine.

The subject matter is concisely and clearly treated in 243 pages, and although the present work adds one more to the long list of books on this subject, its excellence justifies its appearance and it ought to serve a useful purpose in helping the practitioner to handle the much-abused sufferers from this disease.

T. B. F.

## BOOKS RECEIVED.

*Association of American Physicians.* Transactions of the Association of American Physicians. Volume XXIX. 1914. 8°. 679 pages. Printed for the Association. Philadelphia.

*Tics and Their Treatment.* By Henry Meige and E. Feindel. With a Preface by Professor Brissaud. Translated and edited, with a critical appendix, by S. A. K. Wilson, M. A., M. B., B. Sc. 1907. 80°. 386 pages. William Wood & Co., New York.

*Alveolodental Pyorrhea.* By Charles C. Bass, M. D., and Foster M. Johns, M. D. Illustrated. 1915. 8°. 167 pages. W. B. Saunders Company, Philadelphia and London.

*Studies from the Rockefeller Institute for Medical Research.* Reprints, volume XXI. 1915. 8°. 637 pages. The Rockefeller Institute for Medical Research, New York.

*Diarrheal, Inflammatory, Obstructive, and Parasitic Diseases of the Gastro-Intestinal Tract.* By Samuel Goodwin Gant, M. D., LL. D. Illustrated. 1915. 8°. 604 pages. W. B. Saunders Company, Philadelphia and London.

*Collected Papers of the Mayo Clinic, Rochester, Minnesota.* Edited by Mrs. M. H. Mellish. Volume VI, 1914. 1915. 8°. 814 pages. W. B. Saunders Company, Philadelphia and London.



*The Treatment of Fractures.* With Notes Upon a Few Common Dislocations. By Charles Locke Scudder, M. D. Eighth edition, revised, with 1057 illustrations. 1915. 8°. 734 pages. W. B. Saunders Company, Philadelphia and London.

*X-Rays. How to Produce and Interpret Them.* By Harold Mowat, M. D. Edinburgh. 1915. 8°. 204 pages. Henry Frowde and Hodder & Stoughton, London.

*American Pediatric Society.* Transactions of the American Pediatric Society. Edited by Linnaeus Edford La Fétra, M. D. Volume XXVI. 1914. 8°. 362 pages. [American Medical Association Press, Chicago.]

*Modern Aspects of the Circulation in Health and Disease.* By Carl J. Wiggers, M. D. Illustrated with 104 engravings. 1915. 8°. 376 pages. Lea & Febiger, Philadelphia and New York.

*Applied Immunology.* The Practical Application of Sera and Bacterins Prophylactically, Diagnostically and Therapeutically, with an appendix on Serum Treatment of Hemorrhage, Organotherapy and Chemotherapy. By B. A. Thomas, A. M., M. D., and R. H. Ivy, M. D., D. D. S. Five colored inserts and 68 illustrations in text. 1915. 8°. 359 pages. J. B. Lippincott Company, Philadelphia and London.

*Simplified Infant Feeding.* With 75 Illustrative Cases. By Roger H. Dennett, B. S., M. D. With four illustrations. 1915. 8°. 355 pages. J. B. Lippincott Company, Philadelphia and London.

*The Clinics of John B. Murphy, M. D., at Mercy Hospital, Chicago.* Volume IV, No. 3. June, 1915. 8°. W. B. Saunders Company, Philadelphia and London.

*The Medical Clinics of Chicago.* Vol. I, No. 1. July, 1915. 8°. W. B. Saunders Company, Philadelphia and London.

*The Ductless Glandular Diseases.* By Wilhelm Falta. Translated and edited by Milton K. Myers, M. D. With a foreword by Archibald E. Garrod, M. D. (Oxon.) F. R. C. P. (Lond.) F. R. S. With 101 illustrations in the text. [1915.] 8°. 673 pages. P. Blakiston's Son & Co., Philadelphia.

*The Development of the Human Body.* A Manual of Embryology. By J. Playfair McMurrich, A. M., Ph. D., LL. D. Fifth edition, revised and enlarged, with 287 illustrations, several of which are printed in colors. [1915.] 12°. 493 pages. P. Blakiston's Son & Co., Philadelphia.

*Senescence and Rejuvenescence.* By Charles Manning Child. [1915.] 8°. 481 pages. The University of Chicago Press, Chicago, Ill.

*Collected Papers from the Research Laboratory Parke, Davis & Co.* Detroit, Mich. Dr. E. M. Houghton, Director. Reprints. Vol. III. 1915. 8°. 341 pages.

*A Text-Book of Surgery.* By George Emerson Brewer, A. M., M. D. Assisted by Adrian V. S. Lambert, M. D., and by members of the Surgical Teaching Staff of Columbia University. Third and enlarged edition, thoroughly revised and rewritten. Illustrated with 500 engravings in the text and 23 plates in colors and monochrome. 1915. 8°. 1027 pages. Lea & Febiger, Philadelphia and New York.

*International Clinics.* A Quarterly of Illustrated Clinical Lectures and Especially Prepared Original Articles. By leading members of the medical profession throughout the world. Edited by Henry W. Cattell, A. M., M. D. Volume III. Twenty-fifth series. 1915. 8°. 303 pages. J. B. Lippincott Company, Philadelphia and London.

*Diseases of the Arteries, Including Angina Pectoris.* By Sir Clifford Allbutt, K. C. B., M. A., M. D., F. R. C. P., F. R. S., Hon. M. D., LL. D., D. Sc. In two volumes. 1915. 8°. 534; 559 pages. Macmillan & Co., Limited, London.

*Amnesia and Analgesia in Parturition (Twilight Sleep).* By Alfred M. Hellman, B. A., M. D., F. A. C. S. 1915. 12°. 197 pages. Paul B. Hoeber, New York.

*Twelve Lectures on the Modern Treatment of Gonorrhea in the Male.* By Dr. P. Asch. Translated and annotated by Faxton E. Gardner, M. D. Illustrated. 1915. 8°. 104 pages. Rebman Company [New York].

*The Book of the Fly.* A Nature Study of the House-Fly and Its Kin, the Fly Plague and a Cure. By G. Hurlstone Hardy. With an introduction by Halford Ross. [1915.] 12°. 124 pages. Rebman Company, New York.

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## BULLETIN

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## A FURTHER STUDY OF THE DIAGNOSTIC VALUE OF THE COLLOIDAL GOLD REACTION, TOGETHER WITH A METHOD FOR THE PREPARATION OF THE REAGENT.

By SYDNEY R. MILLER, M. D., NATHANIEL D. BRUSH, M. D., JAMES S. HAMMERS, M. D., and LLOYD D. FELTON.

(From the Laboratory of Internal Medicine, Phipps Psychiatric Clinic, Johns Hopkins Hospital.)

### I. INTRODUCTION.

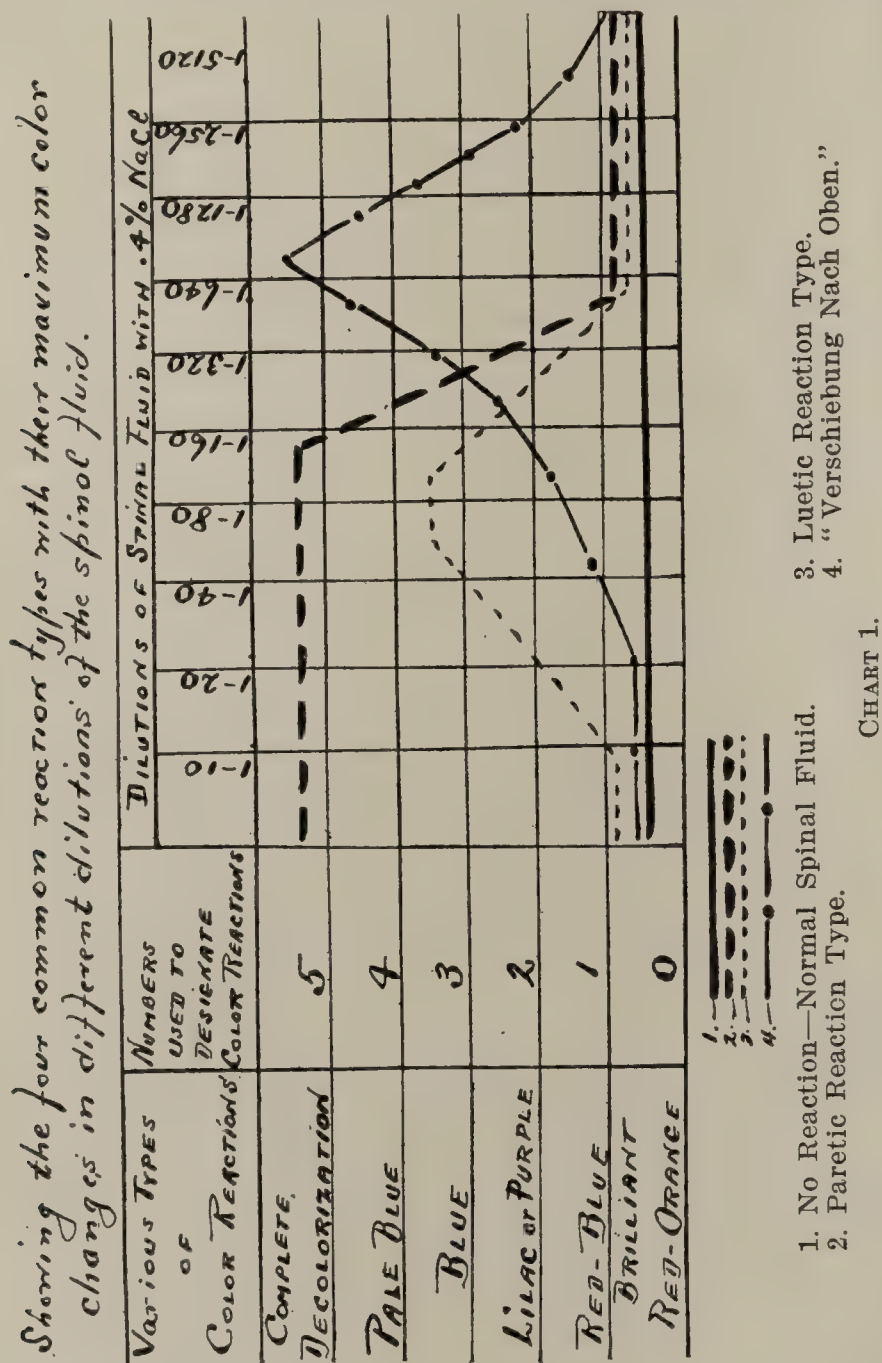
Of all metallic colloidal solutions, those made from gold are probably the most sensitive to the "coagulating" action of electrolytes. This action is a physico-chemical one, in which the electrolyte becomes dissociated into positive and negative ions: interaction with the finely dispersed colloidal particles, which usually carry a negative charge, ensues, so-called neutral aggregates result, and at once conditions are favorable for the precipitating forces of surface tension to become operative. Ultimately the aggregates may reach a size large enough to fall to the bottom of the containing vessel, and cause complete decolorization of the original solution. Depending upon the nature and concentration of the electrolyte present, various alterations of the original dispersion phase may be produced, manifested grossly by color and turbidity changes, ranging from a brilliant clear orange red, through shades of lilac, violet and blue, each increasing in cloudiness in the order named. Much study has been devoted to the conduct of mixtures of two colloids, bearing the same or opposite electrical charges, both in the absence and presence of electrolytes of different valency. Oppositely charged colloids will induce mutual precipitation, provided the correct amounts of each are used. When one colloid is in marked excess, however, the phenomenon of "protective action" is commonly

observed, not merely against spontaneous flocculation but against that due to electrolytes as well. One of the most exhaustive studies of this subject was made by Zsigmondy, who "was able to find a definite measure of the protective action of certain colloids, especially proteins, on the precipitation of gold suspensions by sodium chloride." The degree of protection, moreover, was specific for each protein he examined, as expressed in terms of milligrams of the protein capable of protecting 5 cc. of colloidal gold against 0.5 cc. of a 10% NaCl solution. Having failed by using this general method to distinguish between luetic and normal sera, Lange tried to apply it to a quantitative study of the proteins of the cerebro-spinal fluid. His initial attempts were unsuccessful, for he used distilled water as a diluent, thereby throwing the proteins, particularly the globulins, out of solution, and rendering them inert. When, however, a 0.4% solution of pure sodium chloride was substituted for water, a concentration of sufficient strength to keep the spinal fluid proteins in solution but too weak to cause flocculation of colloidal gold solutions, Lange obtained results as interesting as they were unexpected. Briefly, he observed that normal spinal fluids, suitably diluted with a 0.4% solution of sodium chloride, cause no alteration in suitable solutions of colloidal gold. Abnormal fluids, however, instead of affording some degree of protection, as one might reasonably



expect by reason of their high protein content, cause partial or complete precipitation of colloidal gold, with resultant color changes occurring in curves which tend to be almost specific for certain diseases, particularly those of luetic origin. This apparent specificity is characterized by the occurrence of the maximal color changes within dilution zones, in which the actual amount of the spinal fluid present may be relatively great or exceedingly small. It was quickly noted that fluids from cases of tabes and cerebro-spinal lues gave their maximal reactions within a range of dilutions constant enough to warrant the use of the terms "luetie zone" and "luetie curve"; that fluids from different types of meningitis gave

tenable, however, especially since it has clearly been shown that globulins undoubtedly exert a protective influence upon colloidal gold solutions. Zaloziecki regards it as a form of immunity reaction, in keeping with a growing belief that immunity will ultimately be reduced to concrete terms of colloidal chemistry. Jaeger and Goldstein consider it as a purely physical phenomenon, probably of an electrical nature. Despite this uncertainty as to the exact meaning of the test, practically all observers recognize its specific significance, opinions merely differing as to its practical clinical value. Glaser alone is of the opinion that a general application of the test is impossible, chiefly because of the great difficulty encountered in the preparation of the reagent. Eskuchen, in quite a comprehensive series of cases, endeavored to prove that the gold reaction not only possesses diagnostic value when taken in association with the other well-known cerebro-spinal-fluid tests, but that it actually yields trustworthy results when these are in part or entirely negative. He cites a number of cases to show how true this actually was in his experience, on the basis of which he suggested the adoption of the term "the fifth reaction": and although he correctly insists that it is unwise to rely upon one or two positive or negative reactions in the spinal fluid, but rather upon all tests of accepted value, interpreted in the light of the clinical findings, he none the less claims a degree of specificity and sensitiveness for the gold reaction in luetic diseases of the central nervous system shared by none of the famous "four reactions" of Nonne. Kafka considers the curves seen in cerebro-spinal lues, paresis and meningitis of genuine value: for although the reaction does not always differentiate between cerebral lues and paresis, it is often of tremendous help in determining the type of the disease process. The conclusions reached by Flesch are practically identical with those of Miller and Levy: he regards the test as being much more sensitive and decisive than any of the others, and calls particular attention to the great need of devising a simpler and more certain method for the preparation of colloidal gold solutions. In this country a number of articles have appeared on the subject. Lee and Hinton were much impressed with the clinical value of the test, which, in their experience, was frequently more sensitive than the Wassermann reaction. Weston, Darling and Newcomb obtained typical curves in 34 cases of paresis and similar ones in 3 cases of cerebro-spinal syphilis. The diagnosis in these cases, however, seems somewhat open to question as judged by the brief clinical descriptions given and the fact that in none was there a cell count of over 3 in the spinal fluid. They consider the test a most useful adjuvant to the Wassermann; it is apparently quite as reliable, and, in some instances, by reason of its positive response in the absence of a positive Wassermann, in clinically luetic cases, it has seemed to point toward the possible later appearance of a positive fixation test in the suspected individual. Swalm and Mann doubt the true specificity of the paretic curve, though they observed it in 90% of their cases of dementia paralytica. They believe that the colloidal gold test provides a very delicate method for interpreting the results of the other spinal-fluid reactions, and



"Verschiebung nach oben" or reactions with their greatest intensity in the higher dilutions; and finally, that paretic spinal fluids caused complete flocculation in the first four or six dilutions with such regularity that Miller and Levy<sup>1</sup> suggested the term "paretic curve" and indicated its possible specificity. These three general reaction types are indicated in Chart 1.

This in brief is the history and scientific foundation of a test the exact explanation of which is still unknown. Lange was inclined to regard the various reactions as indicating different qualitative mixtures of proteins, a view not readily



of correcting them when they fail. They observed no characteristic curves in non-luetic psychoses. Solomon and Welles are unable to offer any final conclusions as to the value of the gold solution test in the differential diagnosis of paresis and cerebro-spinal lues: in their experience, cases of undoubted paresis may give atypical reactions and cases not paretic may give the typical reaction. They find the reaction in tabes quite different from that of general paralysis, fairly characteristic of syphilis, but not in itself diagnostic of tabes. Nor is the test of any certain value in cases of congenital lues showing no signs of central nervous system involvement. By suitable studies they were able to show that the gold reaction has the same value in the examination of the cerebro-spinal fluid obtained *post mortem* from the lumbar region, as where examined *ante mortem*, and that the results can be similarly interpreted for diagnostic purposes. Finally, reference should be made to a recent German article by Kaplan of New York, who claims, and with no apparent reference to the earlier similar observations of others, that "the quintessence of his work is that complete *Ausflockung* is characteristic of general paresis." There is a growing, and, in our opinion, a dangerous tendency to ascribe unwonted diagnostic specificity to one or another reaction. We agree with Eskuchen that it is entirely too rash a view to claim that, where a pleocytosis of 100 or over exists, one is *not* dealing with a case of paresis; it is not sound reasoning to say that whenever serological findings favor cerebro-spinal lues and the clinical features point to paresis, it is best to treat the case as one of cerebro-spinal lues; the statement that paresis is excluded, whenever a spinal fluid fails to reduce Fehling's solution strongly and promptly, is entirely too broad, in fact it is untrue. Granted that these statements generally hold, there are undoubted and not infrequent exceptions, and in this very fact there lies great danger both for the patient and the general practitioner himself not skilled in modern laboratory technic or in the interpretation of such works as done by others. One need but study the literature to become convinced of the fact that *no one reaction or group of reactions obtained from the cerebro-spinal fluid is pathognomonic of any syphilitic disease of the central nervous system*. It is undoubtedly true that from an exhaustive analysis of a spinal fluid one may possibly arrive at a correct diagnosis without any knowledge of the clinical condition of the patient from whom the specimen has come. Kafka has been able to construct a number of "type" composite charts, based upon a most elaborate routine examination, which are quite suggestive of certain clinical states, but he strongly denies their absolute specificity and demands the clinical evidence. The assertion of one's ability therefore to centrifuge, as it were, a correct diagnosis from a spinal fluid alone, is, in our opinion, not the evidence of any unusual skill, but rather of the misuse of valuable and scientific methods, comparable to the familiar "snap diagnoses" of immature clinicians. These remarks are made, not so much in a spirit of criticism, as of warning, in view of a growing tendency to divorce laboratory methods from clinical observations. The two are fundamentally complementary: each will lose in value unless they remain so.

The present paper is essentially a continuation of that above referred to, by Miller and Levy. Though convinced of the correctness of their conclusions, it was considered wise to continue observations for a time, having particularly in mind the solution of the following problems:

- (1) The preparation of suitable colloidal gold solutions by some method that was both simple and reasonably certain in its results.
- (2) A clinical method for the standardization of such solutions.
- (3) The incidence of the reaction in cases showing a positive Wassermann in the blood or spinal fluid, or both.
- (4) A comparison of the colloidal gold reaction with the other tests commonly recognized as valuable in the diagnosis of syphilis of the central nervous system.
- (5) The clinical value of the test in:
  - (a) Syphilis of the central nervous system.
  - (b) Extra-neural lues.
  - (c) Miscellaneous non-luetic cases.

## II. ROUTINE EMPLOYED.

Throughout this study, the following routine has been used in every case, where possible: A small number of specimens have been secured from outside sources; in all such instances the spinal fluids have been accompanied by good clinical abstracts, and a statement of the laboratory findings, particularly with reference to the blood serological tests and evidences of spinal-fluid pleocytosis. It is a great pleasure to express our sincere thanks to those who have aided us by sending this valuable clinical material.

(1) *The Wassermann Reaction*.—In accordance with a long established routine, all specimens of spinal fluid and blood have been tested for complement fixation against each of three different antigens. These of necessity have varied slightly from time to time, but for the most part have been of the following nature:

- (a) An alcoholic extract of human heart, plus 0.4% cholesterolin.
- (b) A similar extract, minus the cholesterolin.
- (c) The acetone-insoluble lipoid fraction of either human or beef heart, prepared according to Noguchi's technic.

Suitably and frequently titrated for their antigenic, anti-complementary and hemolytic strengths, these antigens have yielded precisely similar results in the vast majority of cases: the cholesterolized extract has proved the most sensitive of the three, but has never given positive results in non-specific cases. It has invariably been the last to become negative in treated cases. Sera were always inactivated and diluted 1-5, spinal fluids were used just as obtained from the patient. As the result of previous observations, no spinal fluid from a clinically suspicious luetic case was regarded as negative, unless it failed to give fixation, when used in amounts equivalent to 2 cc. with a cholesterolized antigen. A similar standard has been used as a measure of the efficacy of treatment. Most specimens, shown to be positive by the routine method, have subsequently been tested, in four different dilutions, against



each of the three antigens, in order to secure some quantitative idea of their "antibody" content. It has not seemed necessary to record these detailed findings in the present paper. "Complete fixation" has been indicated by the figure 4, complete hemolysis by a cipher 0, and intermediate grades of fixation by the numerals 1, 2 and 3. Complement and amboceptor titrations have been run immediately preceding each Wassermann series.

(2) *Cerebro-spinal-Fluid Examination*.—In addition to the Wassermann reaction, practically every spinal fluid has been subjected to the following examination:

(a) *Cell Count*.—This has always been made as soon after the lumbar puncture as possible, usually within 15 minutes. The Fuchs-Rosenthal counting chamber has invariably been used, and a diluting fluid containing methyl violet, since this makes cellular differentiation a matter of great simplicity.

(b) *Tests for Increased Globulin*. (1) *The Ross-Jones Test*.—This simple modification of Nonne's Phase I Reaction consists merely in layering equal amounts of spinal fluid and a saturated solution of ammonium sulphate. Saturation must be effected at the boiling point.

(2) *Pandy's test* has not received the general use which its simplicity and decisiveness deserve. The reagent consists of a saturated aqueous solution of carbolic acid. To 0.5-1 cc. of the reagent is added one drop of the spinal fluid. The immediate formation of a bluish-white ring or cloud is the evidence of an abnormal protein content. For the most part these two reactions have been parallel. Pandy's reaction, though possessing a sensitiveness not shared by the other, has never given equivocal or misleading results in our experience.

(c) *The Colloidal Gold Test*.—The actual performance of this test is quite easy and requires only about five minutes' time. The procedure is as follows: Into the first of 11 clean dry test tubes, reserved especially for the purpose, put 1.8 cc. of fresh, sterile 0.4% NaCl solution. Into each of the remaining 10 tubes put 1 cc. of salt solution of the same strength. Now add to the first tube, by means of a clean, dry, certified 1 cc. pipette, 0.2 cc. of the spinal fluid to be tested. Mix well. Transfer 1 cc. of the resultant 1 to 10 dilution of spinal fluid to the second tube, and again mix thoroughly and transfer 1 cc. of this dilution to the third tube. Proceed in this manner up to and including the tenth tube. By this method a series of dilutions of the spinal fluid is secured, in geometrical progression, ranging from 1 to 10 to 1 to 5120. Now add to each of the 11 tubes 5 cc. of a suitably prepared and standardized colloidal gold solution, shake each tube thoroughly and set the series of tubes aside for subsequent observations. It will be noted that the 11th tube serves as a salt control, since it contains no cerebro-spinal fluid. Eskuchen recommends the making of readings at the end of 15 and 30 minutes, and again after several hours. It is certainly true that the so-called "initial 5-minute curve" may undergo significant changes during the next 25 minutes. The reaction type observed at the end of half an hour, however, rarely undergoes any further change, save one of intensity. As a result of experience, it soon becomes quite easy to predict what the final readings will be, which in

our work have always been made after the tubes have stood at room temperature over night. Reactions undergo little, if any, change, over a period of several weeks, provided evaporation and exposure to direct sunlight are guarded against. In like manner, any given fluid, if kept sterile and on ice, will produce the same colloidal gold curve over a period of time, the exact length of which is unknown. This knowledge is of particular value since it easily enables one to keep a control fluid on hand. Spinal fluids contaminated with blood cannot be used except for a Wassermann test.

Misleading reactions will be avoided by delivering the spinal fluid directly into dry, sterile test tubes through an iridio-platinum needle, cleaned with alcohol and ether, and sterilized by means of hot air.

As regards the methods of recording our results, arbitrary signs have been chosen and used as follows:

(a) Wassermann reaction: see above description.

(b) Cell count: the calculated number per cmm. has always been given: 10 cells or more per cmm. have constituted a pleocytosis.

(c) Globulin tests have been recorded as follows:

Negative . . . . .	0
Borderline . . . . .	±
Positive . . . . .	+
Strongly positive . . . . .	++

(d) Reference to Fig. 1 will show what numerals have been used to denote the various types of color changes seen in a positive gold reaction. Entry may either be made by means of such numbers, or by the construction of a curve upon an appropriate chart. The one shown in Chart 2 has been most satisfactory: filled out in the laboratory, these charts are ultimately incorporated in the clinical histories of the respective patients.

The colloidal gold curve represented graphically in the above chart would have the following numerical representation: 5555542100.

(3) *The Clinical Findings*.—At the risk of what may seem an unnecessary repetition, we desire to emphasize once more the fundamental importance of correlating, in every case, the laboratory findings with the clinical history and physical signs. Despite the apparent certainty of making a correct "laboratory diagnosis," in a number of instances we have found it safest and most instructive to take nothing for granted. Accordingly, we have consistently refused to examine specimens not accompanied by suitable and sufficient clinical data. Moreover, where the laboratory findings have appeared to be at variance with the data thus supplied, we have endeavored, not only to repeat the tests on second specimens, but also to have the patient gone over again thoroughly by one or more observers. It has been interesting to note in this fashion the frequency with which certain conditions, particularly early cases of dementia paralytica, are overlooked in the medical wards of a busy hospital, and how often the condition is called "cerebral lues," a diagnosis usually based upon a few physical signs and a positive Wassermann, with little or no attempt made to detect the characteristic or incipient mental and memory defects. The importance of this cannot be overestimated, since



there is some evidence to show that, if diagnosed early enough, cases of paresis can be arrested, if not indeed cured, by suitable therapy. We have observed at least one such case. The instances in which laboratory results have been proved wrong or consistently anomalous have but served to convince us all the more of the great need of developing laboratory men from the ranks of carefully trained clinicians. Whenever it has been

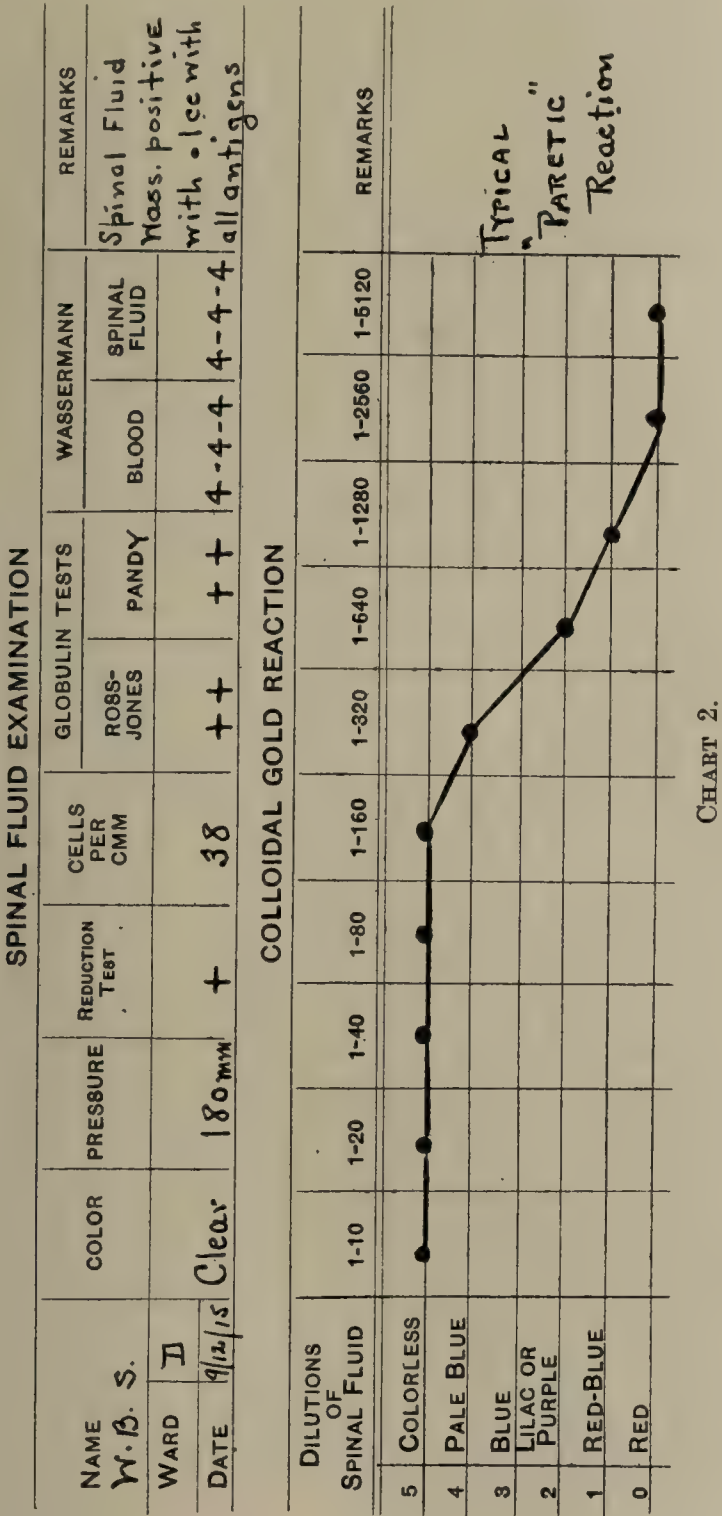
(1) *Lange's Method* (a modification of Zsigmondy's).—To 1000 cc. of purest, freshly distilled water, add 10 cc. of a 1% solution of gold chloride, and a like amount of a 2% solution of  $K_2CO_3$ . The solution is heated rapidly until it almost boils; at this point, and while stirring vigorously, add 10 cc. of a 1% solution of formalin. The previously colorless solution should at once assume a clear intense red (satt rot) color, must be absolutely clear and show no superficial smoky shimmer. Lange advises making up a 100 cc. lot first, to make certain of the purity of the water. He insists upon the use of Jena glass throughout, the avoidance of any rubber connections in the still, and points out with what great care all utensils must be cleaned.

(2) *Eicke's Method*.—The author recommends the following technic:

- Doubly distilled  $H_2O$ .....1000 cc.  
 $AuCl_3$ —1% solution ..... 10 cc.  
Dextrose—5% solution ..... 5 cc.

This solution is heated to 90-95° and then a 5% solution of  $K_2CO_3$  is added, a drop at a time, until the required color is secured. Eicke also uses Jena glass and insists upon scrupulous cleanliness. It will be seen that the only essential difference between the two methods is that in one formaldehyde is the reducing agent, in the other, dextrose. The advantage claimed for the latter is that it is less explosive in its action, that reduction, therefore, proceeds more slowly, and as a result satisfactory colloidal solutions are obtained more consistently than by the formalin method.

Despite the apparent simplicity of each of these methods, the opinion seems unanimous that suitable colloidal gold solutions are extremely hard and uncertain to prepare. Each author, in turn, has added a refinement in technic, or slight modification of the original, claiming better results therefrom. Glaser believes the essential difficulty comes from the use of glass-ware insufficiently cleaned, and gives a most elaborate procedure to avoid such trouble. He is of the opinion that the carbon dioxide tension in the water modifies the final result, and thinks therefore that the formalin is best added at boiling temperature. Flesch, using Lange's method, could not obtain good solutions unless he used much less than 10 cc. of 1% formalin, generally 2-3 cc. He encountered great difficulty with Eicke's technic. In fact his experiences were so trying that he urged the wisdom of having some chemical firm manufacture the reagent on a large scale, since only by such a measure could the test ever receive wide clinical application. Matzkiewitsch, who has used colloidal gold in the Abderhalden reaction, gives the address of one such firm. Kafka asserts that the preparation of colloidal gold is "uncommonly hard"; and that one often fails in making it, even when every care is exercised. He threw out every solution that showed even the faintest tinge of blue. Eskuchen obtained satisfactory results with Eicke's method, *but frequently made beautiful solutions which would not react*, for no known reason. He insists upon the use only of "hoch rot" or "satt rot" solutions. Comparative studies made by him showed that the blue or purple fluids gave comparative curves with abnormal fluids, whereas, with



possible, the initial diagnosis in a case has been confirmed either by prolonged observation, subsequent physical and laboratory examinations, or by autopsy.

III. THE PREPARATION AND STANDARDIZATION OF COLLOIDAL GOLD.

Since the introduction of this test, two general methods have been used by most observers, for the preparation of colloidal gold. Though these methods are quite similar in principle, and require practically the same reagents, both are given here. Fuller details may be obtained in the original articles.



normal spinal fluids, blue solutions give changes when "hoch rot" ones do not. He calls particular attention to the fact that the most brilliant and beautiful solutions are by no means always the best. He recommends testing each new colloidal solution against a normal, a tabetic and a paretic spinal fluid, and every spinal fluid against two satisfactory gold solutions. Lee and Hinton, after some study, came to the conclusion that "the preparation of a good translucent 'high red' reagent is largely dependent upon freeing the distilled water from the gases in solution." Their experience was that, unless the color change is almost instantaneous after the addition of the formalin, the resulting reagent will be poor. Swalm and Mann advise the boiling of all cork connections used in the distilling apparatus. Kaplan favors Lange's technic: he employs 0.75% formalin instead of 1%, and keeps the beakers, in which the reagent is prepared, in distilled water for 24 hours before use. Like all others, he finds that the use of rubber connections is not advisable. Unlike Lee and Hinton, he noted that the color change comes gradually, as a rule, in good colloidal gold solutions. All the authors above cited have used an all-glass distilling apparatus. Miller and Levy, using Lange's method, expressed the opinion that, "provided due care is exercised in the preparation of the water and the cleaning of the glass-ware, satisfactory colloidal solutions can always be obtained by the method above described." This statement seemed justified in our later experience, until suddenly it became apparently impossible for us, though using the same technic and reagents, to prepare good gold solutions. Even after it was found that the glass still was giving off colloidal silica, the trouble continued, though with no demonstrable consistency. This experience was further complicated by the not infrequent discovery that *beautiful solutions, answering all other criteria, were absolutely inert when tested against a known paretic fluid*. In view of the fact, therefore, that there has been a great deal of difficulty in making colloidal gold solutions suitable for diagnostic purposes; that there has been a lack of uniformity in the method and chemicals used and consequently in the results obtained; that many workers have been utterly unable to prepare a good gold solution; and, finally, for the reason that the characteristic reaction in a certain group of diseases of the central nervous system is of such inestimable diagnostic value, a considerable amount of attention has been devoted to an attempt to overcome these difficulties. The aim has been to perfect a technic by which a gold solution of known suitable electrolytic stability and diagnostic value could readily be made.

In the choice of a method for the preparation of such a gold solution—by reduction, oxidation, hydrolysis, condensation, or chemical and electrical dispersion—reduction seemed to be the most practicable, because of its simplicity and the greater stability of the resultant colloidal solutions. This method requires the careful observance of three physico-chemical conditions: (1) a dilute solution of a reducible gold salt in the presence of an alkali; (2) a reducing agent, and (3) a correct temperature at which the reduction takes place. The question of the proportion of the chemicals employed and the

optimal temperature for reduction finds its true analogue in the development of a photographic plate. In this process, solutions of an alkali, the accelerator, and of a reducing agent, the developer, are used at a correct temperature. That these three factors are reciprocal in their relation to each other, within certain definite limits, is shown by the following equations, in which these abbreviations have been adopted:

Alk. = Alkali.	Amt. = Amount.
Red. = Reducing agent.	< = Less than.
T° = Temperature.	—
Opt. = Optimal.	> = Greater than.

#### A. CONSTANT OPT. T°.

- |                                       |  |
|---------------------------------------|--|
| (1) Alk. + Red. in opt. amts.         | = Prompt development<br>—good sharp plate. |
| (2) Alk. < opt. amt. + opt. amt. Red. | = Poor development—<br>plate lacks detail. |
| (3) Alk. > opt. amt. + opt. amt. Red. | = Development too<br>rapid—foggy plate.    |
| (4) Alk. opt. amt + < opt. amt. Red.  | = Same as No. 2.                           |
| (5) Alk. opt. amt. + > opt. amt. Red. | = Same as No. 3.                           |

#### B. VARIABLE T°.

- |                                 |   |   |
|---------------------------------|---|---|
| (6) Alk. + Red. in opt. amts. + | { | T° < opt. = Too rapid<br>development<br>—no detail. |
|                                 |   | T° > opt. = Under devel-<br>opment.                 |

#### A. REACTIONS WITH AuCl<sub>3</sub> IN CONSTANT AMT.

T° CONSTANT AND OPT. = 90° CENT.

- |   |  |
|---|--|
| (1) AuCl <sub>3</sub> + Alk. < opt. amt. + opt. amt. Red. | = Incomplete<br>reduction<br>or none at<br>all.                                    |
| (2) AuCl <sub>3</sub> + Alk. > opt. amt. + opt. amt. Red. | = Reduction<br>too rapid—<br>coarse dis-<br>persion<br>purple-<br>brown sol.       |
| (3) AuCl <sub>3</sub> + opt. amt. Alk. + Red. < opt. amt. | = Incomplete<br>reduction<br>often with<br>formation<br>of "Purple<br>of Cassius." |
| (4) AuCl <sub>3</sub> + opt. amt. Alk. + Red. > opt. amt. | = Reduction<br>too explo-<br>sive—sol. is<br>yellow-red<br>—not trans-<br>parent.  |

#### B. AuCl<sub>3</sub>, ALK. AND RED. IN CONSTANT AND OPT. AMTS.

T° VARIABLE, BUT AT LEAST 2° ABOVE OR BELOW OPT. T°.

- |  |  |
|--|--|
| (1) AuCl <sub>3</sub> + Alk. + Red. at T° > 90° C. | = Poor sols.<br>—due to<br>too rapid<br>reduction. |
| (2) AuCl <sub>3</sub> + Alk. + Red. at T° < 90° C. | = Poor and<br>slow reduc-<br>tion.                 |

When all other factors are constant and optimal, variations in the amount of gold chloride result in the production of



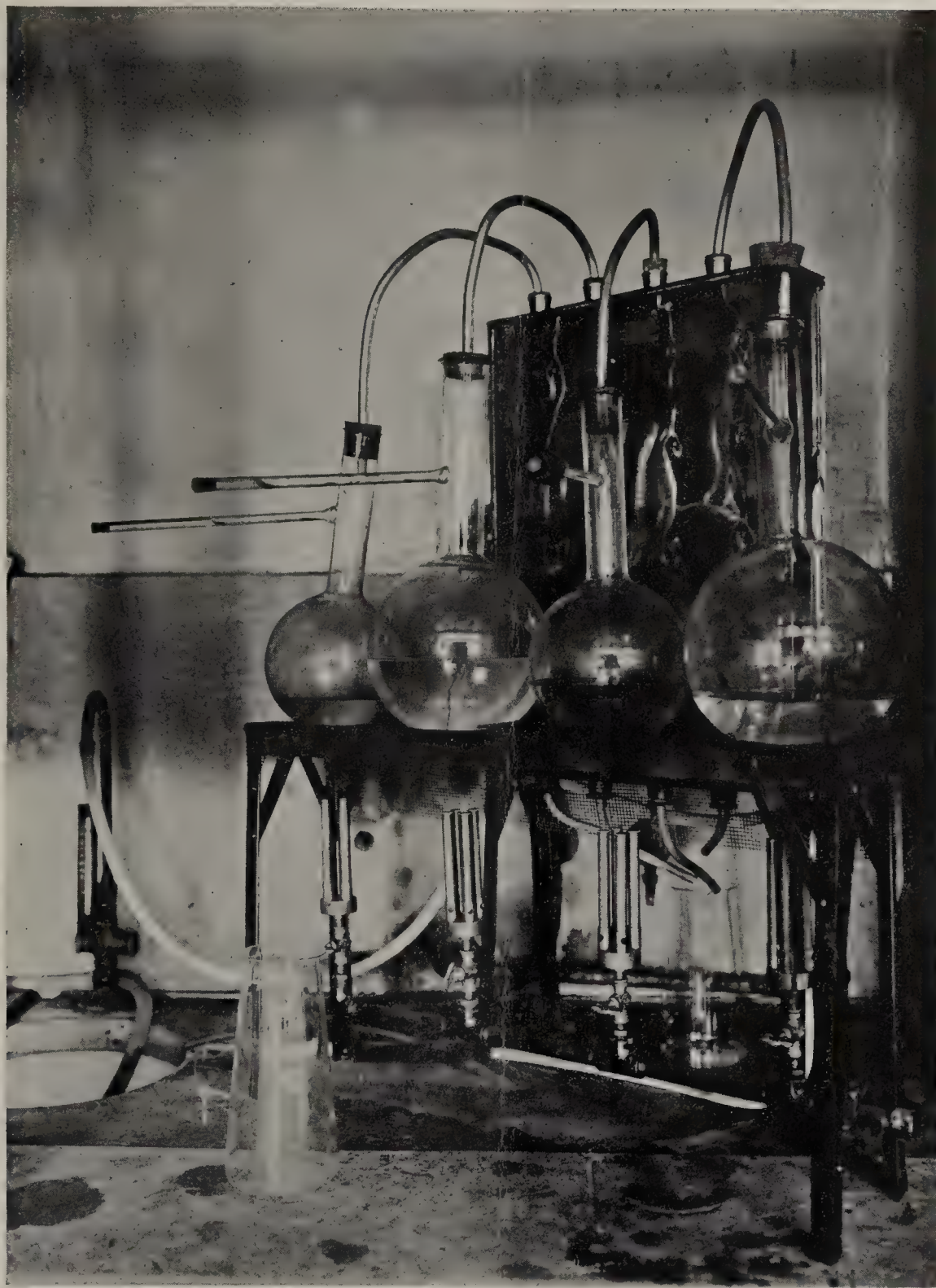


FIG. 1.—Type of distilling apparatus used in this work, showing large distilling flasks and block tin condensing tubes, all delivering triply distilled water into the same Jena glass beaker.



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solutions of different degrees of color intensity, small amounts making a light-colored solution, large amounts deep, dark red ones. An excess of gold acted, therefore, a great deal like an excess of the reducing agent, producing a fairly coarsely dispersed yellowish non-transparent red solution. The above observations are true only after eliminating all technical errors, particularly the use of impure water, dirty glass-ware, solutions inaccurately made or allowed to stand too long.

Though almost any reducing agent can be employed—such as metol, hydroquinone, pyrogallol, glucose, acids, and others—formaldehyde seemed to give the most dependable results. However, after giving it a fair test, it became evident that *its reducing power is too often explosive, the resulting solutions having a yellowish shimmer*. Oxalic acid takes the part of a slow reducing and clarifying agent in the making of a photographic negative; it seemed worth while, therefore, to note its action in the preparation of colloidal gold solutions. It was found that, when very small quantities of dilute oxalic acid solution were added before the formaldehyde, most beautiful clear deep orange or salmon red solutions resulted. Furthermore, a large amount of oxalic acid without the subsequent addition of formaldehyde made clear “satt rot” colloidal gold solutions, but these invariably required further treatment before they were of any use clinically.

The method here described has been so successful that it has seemed advisable to describe in detail the apparatus and reagents required, the methods for cleaning the glass-ware, distilling the water, the successive steps in making the colloidal gold, and, finally, its electrolytic standardization.

#### A. THE APPARATUS NEEDED IS AS FOLLOWS.

A good still equipped with Jena glass distilling flasks and either glass or block tin condensing tubes. There should be no rubber connections.

Jena beakers, 100 to 2000 cc. capacity.

Jena Florence flasks for collecting the distilled water.

Graduates, 25 to 100 cc.

Pipettes, 1 to 5 cc., to be used for this work only.

White enameled pan for boiling up the glass-ware.

Brushes for cleaning the beakers and other glass-ware.

Large Bunsen burner, tripod and wire gauze with an asbestos center.

One thermometer (Jena glass).

Thick-walled test tubes.

#### B. THE REAGENTS USED AND THE STRENGTH OF EACH.

##### (1) *The gold solution:*

AuCl<sub>3</sub>—Merck's yellow crystals hermetically sealed in brown glass ampoules 1 gram.

Water triply distilled, up to.....100 cc.

This stock solution is kept well stoppered in dark glass bottles away from any bright light.

##### (2) *The alkaline solution:*

Merck's Blue Label Potassium Carbonate (desiccated) ..... 2 grams.

Water triply distilled, up to.....100 cc.

##### (3) *The reducing agents:*

a. Formaldehyde, Merck's 40% stock solution, highest purity..... 1 cc.

Water triply distilled, up to..... 40 cc.

b. Oxalic acid, Merck's Blue Label, Crystals ..... 1 gram.

Water triply distilled, up to.....100 cc.

*Solutions No. 2 and No. 3 must be made up immediately prior to use.*

##### (4) *Bichromate cleaner for glass-ware:*

Potassium Bichromate (powdered)... 200 grams.

Water distilled, up to.....1500 cc.

Sulphuric acid conc..... 500 cc.

The potassium bichromate should be well dissolved before the sulphuric acid is added. If this solution is reserved for cleaning glass-ware only, it can be used repeatedly.

#### C. TECHNIQUE FOR CLEANING GLASS-WARE.

The cleaning of the glass-ware preliminary to making the colloidal gold has been quite a problem. However, after trying out four or five different methods, the following has been adopted as best for eliminating dirty glass-ware as a source of error.

The beakers are boiled up in an ivory soap solution (one-half cake to about 5 liters of water) for 30 minutes. One beaker at a time is then removed, and thoroughly brushed under hot tap water. After being rinsed for 5 minutes in running water, the beaker is filled with some hot bichromate cleaner, and left standing for at least one-half hour. When needed, the beaker is emptied and washed again in running water for 5 minutes. This is followed by a careful rinsing with ordinary distilled water, and finally with triply distilled water. The beaker is now clean and ready for *immediate use*. The pipettes, the graduates and the flasks are cleansed in exactly the same way, except they are well washed with hot water and soap, but not boiled. The three errors most commonly made in cleaning are: (1) insufficient brushing; (2) failure to wash out all of the bichromate solution; and (3) allowing the beaker to dry in the air before being used.

#### D. TECHNIQUE FOR SECURING DISTILLED WATER.

It has been observed that silicates are often dissolved out of glass condensing tubes, particularly after long use, thus rendering the water unsuitable for preparing colloidal gold solutions. We have employed, therefore, a still in which block tin condensing tubes have been substituted for glass (Fig. 1). This apparatus is merely a Kjeldahl condenser modified to suit the requirements of this work, for which it has proved eminently satisfactory.

A good colloidal gold solution can be made at times with doubly or even singly distilled water by using the technique given in this paper. Repeated observations, however, have convinced us that water three times distilled is the safest to use in preparing solutions which must meet the requirements described below. The extra time consumed in distilling is nothing when compared with the certainty of results.



In carrying out the distillation, the following plan has been used: the first distillate is taken from an ordinary laboratory Stokes still. This is immediately poured into clean Jena distilling flasks. The first 200 cc. of the second distillate is used to rinse out the collecting flask, and after the remainder of the second distillate has been collected, it is transferred to a second Jena distilling flask. The collecting flask for the third distillate is rinsed with the first 200 cc., as was the second. In like manner each distilling flask is washed out with some of the new lot of water that is to be put into it. The water should be used as soon after its last distillation as possible.

#### E. TECHNIQUE FOR THE PREPARATION OF COLLOIDAL GOLD.

The process is very simple. Good results depend more upon the preparatory steps above outlined than on the actual procedure here described. A beaker, rinsed out with a portion of triply distilled water, is filled to a liter mark, and after the temperature has been gradually raised to about 50° C. the gas is turned on full. When the temperature has reached 60°, 10 cc. of the 1% gold solution and 7 cc. of the 2% potassium carbonate are added. The solution should remain perfectly clear. At 80° C., while stirring with a clean thermometer, add slowly 10 drops of oxalic acid. Frequently the solution now turns a very delicate bluish pink, which may depend either upon the rapidity of the rise in the temperature, a slight excess of alkali, or the presence of some unknown impurities. An excess of alkali nearly always gives a pink coloration immediately after the oxalic acid is added, and consequently the latter serves as a delicate indicator of the fact that an excess of  $K_2CO_3$  has been added.

Usually, when such an excess has not been employed, the entire solution remains colorless when it has reached a temperature of 90° C. At this point the gas is turned out, or the flame is withdrawn, and, while stirring, 5 cc. of 1% formaldehyde is slowly added, a drop at a time. If a pink color makes its appearance before all the reducing agent has been added, *stop at once*, for reduction will continue to the final end-point, which is marked by the production of a beautiful brilliant clear orange-red solution. We have observed that *the best solutions are those in which the color changes develop slowly*.

The following procedures may be resorted to in cases where, for one reason or another, the solutions behave in an atypical manner:

(1) When the solution becomes very definitely pink after the addition of the oxalic acid, add formaldehyde slowly, but only until an intensification of the color is noted.

(2) Should no color appear after the lapse of some minutes, during which the temperature of the solution has been kept at 90° C., add more formaldehyde, drop by drop, until a pink color develops. It is not wise to use more than 3 cc. of this additional reducing agent.

(3) Should there still be no evidence of reduction, stir the solution vigorously, and add some of the 2%  $K_2CO_3$ , a drop at

a time. Usually one drop, or a few at the most, will call forth a faint pink tinge, which is the signal to stop.

Although it is possible to make up a liter or more at one time, it is always advisable to prepare only about 200 cc. first. From the result of this preliminary test is secured the following information:

(1) Whether the water is free from impurities that would vitiate good results.

(2) Whether the correct amount of alkali has been used or not. For reasons not known, *the same amount of alkali does not work equally well with every lot of distilled water*.

Using this method, we have been able to make over one hundred different lots of colloidal gold with different stock solutions, different water, and on different days, without a single failure. We feel confident, therefore, that if the general basic principles are kept in mind, and if the technique is followed closely, anyone can readily prepare very satisfactory colloidal gold solutions.

In summary, the technique for preparing one liter of colloidal gold is as follows:

Heat 1000 cc. of triply distilled water over a good Bunsen burner. At 60° add 10 cc. of a 1% solution of gold chloride and 7 cc. of a 2% solution of potassium carbonate. At 80°, while stirring briskly, add 10 drops of a 1% oxalic acid solution. At 90° C. remove the burner and, while stirring, add 5 cc. of formaldehyde (1-40) or enough to produce an initial pink color.

Having made beautiful clear solutions by means of the above technique, we were confronted with the fact that a great number of them would not be precipitated by a known paretic spinal fluid, and those that were precipitated showed the change with varying degrees of rapidity. There are two general types of metallic solutions, the "protected" and the "non-protected." By the former is meant one in which no agglutination takes place after the addition of any amount, or at least of a large amount, of any electrolyte. The non-protected type is one in which agglutination occurs in the presence of very small amounts of electrolyte. In working over 300 different lots of colloidal gold, we found that, for all practical purposes, a non-protected solution was one that would be completely precipitated by 1.7 cc. of a 1% sodium chloride solution in one hour's time. It was comparatively easy therefore by this method to eliminate the protected solutions. It was difficult to understand, however, why non-protected solutions required different amounts of an electrolyte or different lengths of time with the same amount of electrolyte to produce the same end-reaction. In attempting to answer these questions, a series of experiments brought out the following facts: (1) There was a considerable difference in the alkalinity and acidity of the various colloidal gold solutions. (2) The alkaline solutions were almost entirely inert to the electrolytic forces of a positive spinal fluid. (3) A slightly acid solution gave a typical reaction with a paretic spinal fluid, but also a very typical reaction in the luetic zone, with a known negative fluid, and merely an intensification of this luetic zone reaction with a fluid from a case of cerebrospinal syphilis. (4) A strongly acid solution gave





Showing three different types of colloidal gold solutions. All are beautifully transparent when examined with direct light. Viewed from any angle, A and B are absolutely clear, while C shows a superficial yellowish shimmer and is cloudy when looked at from above. Such a solution is unsatisfactory.

Solution A is of the optimal brilliant red-orange shade.

Solution B is of the "satt rot" color referred to especially in the German literature. Both are suitable for use, so far as their color is concerned.



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very little, if any, reaction with a known positive spinal fluid, and an atypical one with a known normal fluid. This fact probably gives the explanation of Kafka's experience, which was that some solutions gave no reaction with a known positive fluid and an atypical reaction with a known negative spinal fluid. (5) Finally, it was found that a neutral colloidal gold solution produced the typical reactions with a known paretic and luetic spinal fluid, but never induced color changes with a known negative fluid. This last observation seemed to give the key to the situation, for it was now apparent that *any solution to be of value in this test must be of a "non-protected" type, and of a neutral reaction.* The first requirement is comparatively easy to meet, if enough care is taken in regard to cleanliness. The following method has been found satisfactory for establishing the neutral point of any gold solution:

The indicator used is alizarin red, made up in a 1% solution in 50% alcohol. The color produced by this indicator with an alkaline colloidal gold solution is a purplish red. The neutral point is of a brownish-red tinge, while with an acid solution it gives a lemon-yellow color. To ascertain whether a given solution is alkaline, neutral or acid, a preliminary test is made by adding two drops of the indicator to a test tube containing about 5 cc. of the gold solution. After the color produced has been noted, 10 test-tubes are set up in a rack, and 1 cc. of freshly distilled water is put into each. Depending upon whether the solution is acid or alkaline, add 1 cc. of N/50 NaOH or N/50 HCl to the first tube. Proceed then as in diluting the spinal fluid in the regular colloidal gold test, mixing well and drawing 1 cc. from each preceding tube and adding it to the next one, omitting only the tenth tube. Now add to each tube two drops of the indicator and 5 cc. of the gold solution to be tested. The amount of acid or alkali in each successive tube will be as follows: 0.5 cc., 0.25 cc., 0.125 cc., 0.0625 cc., 0.03125 cc., etc., each tube having exactly one-half the amount of the preceding one.

Having determined in this manner the amount of N/50 acid or alkali necessary to render 5 cc. of colloidal gold neutral, the total amount required to neutralize the entire solution can readily be estimated. Thus, for example, suppose the neutral point is reached in the 3d tube of the series, and the total amount of the colloidal gold solution is 1000 cc.; then

$$\frac{0.125 \text{ N/50 acid or alk.}}{5} \times 1000 = 25 \text{ cc.,}$$

or in other words, add 25 cc. of N/50 alkali or acid, as the case may be. The acid or alkali should be added very slowly, while the solution is well agitated; otherwise, some precipitation is apt to occur. It is unwise to neutralize solutions of colloidal gold until they are at least 48 hours old.

Observations on the changes which take place in good colloidal gold solutions after they have stood for some time have revealed the following facts: (1) A solution kept in a bright light loses its orange red tint and becomes almost the red-blue of a No. 1 reaction. (2) Solutions, if kept in a dark place, retain their red orange color for a long time. (3) Solutions, when first made, are apt to be slightly acid, turning alkaline after standing for varying lengths of time. (4) Even

after neutralization, they tend to become alkaline, and therefore inert to a certain degree. Accordingly, it is advisable to keep all solutions in a dark place, and test them from time to time to determine their reaction.

Kaplan has advocated the control of the color of the colloidal gold by means of an arbitrary mixture of Congo red and alizarin in an alkaline solution. Having noted the fact that variations occur in the color of the solutions made by the technique here given, some experiments were made on them, with the following results: As long as a solution was absolutely clear and neutral in reaction, and of the non-protected type, the exact color made no difference in its power to produce typical reaction curves. The orange red solutions gave better-looking tests, but the final results were the same, regardless of the many shades of color in the different solutions. After prolonged standing, a good solution may occasionally change to a color almost the same as that in a No. 1 reaction in the colloidal gold test. When such a change is noted, the fluid should be thrown away.

The following are suitable standards for a satisfactory colloidal gold solution:

- (1) It must be absolutely transparent and preferably of a brilliant red orange, or salmon red color.
- (2) Five cc. of the solution must be completely precipitated by 1.7 cc. of a 1% sodium chloride solution in the time interval of one hour.
- (3) The solution must be neutral in reaction on the day on which it is used.
- (4) It must give a typical reaction curve with a known paretic cerebro-spinal fluid.
- (5) It must produce no reaction greater than a No. 1, with a known normal cerebro-spinal fluid.

#### IV. CLINICAL MATERIAL.

The present report is based upon the examination of 300 spinal fluids that have been subjected to the routine study outlined in Sec. II. For numerous reasons it has seemed best to record the results in a detailed form. This is particularly important, in order to facilitate an analysis of the incidence of the various reactions in different types of diseases. Moreover, in no other way can the exact results of the gold test be clearly conveyed to one unfamiliar with its reactions. It was felt that, for those engaged in studies on this particular subject, the following tables would prove more valuable than mere statements of recorded findings; while for those interested more in the conclusions reached than the data on which they are based, a later section would suffice.

The colloidal gold reaction has given the most consistent and valuable results in cases of general paresis. Characteristic curves were given by 127 of the 130 fluids tested. Of the three atypical reactions, one (No. 20) occurred in a very early but undoubted case of paresis, a second (No. 160) was probably due to the use of an old and infected spinal fluid, while the third (KC) was an absolutely normal curve given by the fluid of a case which had received vigorous intraspinal therapy. This is the only instance we have observed in which the spinal







TABLE II.—TABES DORSALIS.

Case Number.	Ward.	Cells per cmm.	Tests for increased Globulin.		Colloidal Gold Reaction.	Wassermann.									Remarks.
			Ross-Jones.	Pandy.		C. S. F.			Blood.						
						An-tigen.			An-tigen.						
						A	B	C	A	B	C				
19	M	72	+	+	4443210000	4	4	4	4	4	4	G. P. (?)			
39	C4	41	+	+	1222100000	4	4	4	4	4	4				
73	C3	1	0	0	1123211000	0	0	0							
46	M	3	0	0	1222100000	0	0	0	4	4	4				
75	G	18	++	++	5545544200	0	0	0	4	4	4				
79	C4	70	+	++	4445542000	4	4	4	4	4	4	G. P. (?)			
83	G	12	+	+	1235532100	4	4	4	4	4	4				
90	G	25	+	+	2334431000	2	3	1	4	4	4				
144	F	3	+	+	4445443210	4	4	0	4	4	4				
152	F	7	0	++	3334310000	0	0	0	4	4	4				
123	E	1	+	+	4444310000	4	4	4	0	0	0	G. P. (?)			
253	E	28	+	+	1123310000	4	4	4							
263	E	28	++	++	4433321000	4	4	4	4	4	4				
268	F	15	+	+	4433321000	4	4	4	4	4	4				
292	BC	32	+	+	4443322210	4	4	4							
307	F	10	+	+	2234413100	4	4	2	0	0	0	Treated case.			
318	F	26	+	+	2223332100	4	0	2	0	0	0				
332	F	26	+	+	1223210000	3	3	3	0	0	0				
336	F	24	++	++	5555431000	4	4	4	0	0	0				
338	F	2	0	0	0000000000	0	0	0	0	0	0				
342	F	1	+	+	3322221000	0	0	0	0	0	0	G. P. (?) Thoroughly treated case. Death after 606. Many treatments. No physical signs of G. P. After many treatments. " " "			
347	C1	8	++	++	4443220000	4	4	4							
350	M	133	++	++	5555543000	4	1	3	0	0	0				
351	M	10	++	++	0000000000	0	0	0	0	0	0				
352	M	1	++	+	0002200000	0	0	4	0	0	0				
358	F	32	++	++	5555544300	4	4	4	4	4	4	Well marked tabes. " " " No G. P. Many intra-spinous treat-ments. Many intra-spinous treat-ments.			
360	F	33	+	+	5544444000	0	0	0	0	0	0				
367	H	1	0	++	4444320000	3	1	0							
375	M	6	+	+	1111111000	0	0	0	0	0	0				
379	F	11	++	++	4433332000	4	1	0	4	4	4				
327	E	10	+	+	2222121000	0	0	0				Tabetic bladder. Many treatments.			
340	BC	9	+	+	1111000000	3	0	0	0	0	0				
353	F	4	++	+	3333300000	4	1	3	4	4	4				

\*Not done.

fluids have seemed to give gold reactions of a No. 4 intensity perhaps more frequently than any others. These reactions are not, however, in any way characteristic or diagnostic of this condition. Reference to the table will show that some of these reactions occurred in fluids having a normal cell count, a negative Wassermann and equivocal globulin tests.

TABLE III.—CEREBROSPINAL LUES.

Case Number.	Ward.	Cells per cmm.	Tests for increased Globulin.		Colloidal Gold Reaction.	Wassermann.						Remarks.
			Ross-Jones.	Pandy.		C. S. F.			Blood.			
						An-tigen.	An-tigen.	An-tigen.	An-tigen.			
									A	B	C	
2	OS	8	++		1221000000	0	0	0	4	4	4	G. P. (?)
7	W2	8	+		1231000000	0	0	0	4	4	4	
26	OS	4	+	+	1221000000	0	0	0	0	0	0	
55	W3	141	++	++	5555543210	4	4	4	4	4	4	
80	G	44	+	+	1123211000	0	0	0	4	4	4	Diagnosis revised to G. P. (?)
132	M	4	0	0	2233432100	0	0	0	4	4	4	
136	M	5	0	0	3345554310	0	0	0	0	0	0	
177	F	4	+	+	5554430000	4	4	4	4	4	4	
244	F	*	+	+	3444332210	4	4	4	4	4	4	Bulbar lues ; G. P. (?) Diagnosis (?). No history of lues. Cerebral gumma.
259	G	14	+	+	2233321000	4	2	0	4	4	4	
308	OS	3	+	+	5544432000	4	4	2	4	4	4	
77	G	*	+	+	5555442100	2	2	2	4	4	4	
334	F	1	++	++	0000000000	0	0	0	0	0	0	
343	F	1	+	+	1111000000	0	0	0	0	0	0	
346	OS	45	++	++	4432210000	4	4	4	4	0	4	

\*Not done.

Spinal fluids from 14 different cases of cerebrospinal lues were examined. Though included in this series, cases 55 and 177 are most certainly instances of paresis; clinically, the diagnosis could not be made absolutely, but, when taken in association with the laboratory findings, the evidence was strongly in favor of dementia paralytica. Paretic gold curves have been observed in cases where there were no signs or

symptoms of general paralysis, but in our experience these are unusual exceptions. Of the remaining 12 cases, the blood Wassermann was positive in 9, the spinal fluid in 5 instances. It will be noticed that the cell counts in all cases except one were under 100, and many were within the limits of normal. In six of these the additional negative spinal fluid serological findings would seem to throw these cases into the so-called "Plaut type." This and the acellular form of cerebrospinal lues have by no means been as infrequent, in our experience, as the sections in Kaplan's book would lead one to suppose. Ten of the 12 cases gave typical "luetie zone" gold reactions that varied between 1111000000 and 334554310. Cases 308 and 77, clinically not suspected of paresis, showed decolorization in the first two and four tubes, respectively.

TABLE IV.—TERTIARY LUES.

Case Number	Ward.	Cells per cmm.	Tests for increased Globulin.		Colloidal Gold Reaction.	Wassermann.						Remarks.
			Ross-Jones.	Pandy.		C. S. F.			Blood.			
						An-tigen.			An-tigen.			
						A	B	C	A	B	C	
135	W1	1	+	+	2234555300	0	0	0	4	4	4	Wass. pos. in double amounts.
248	M	3	++	++	0000000000	0	0	0	4	4	4	
158	C3	6	+	+	2343321000	2	2	2	4	4	4	
16	M	82	+	+	1221000000	4	4	4	4	4	4	
283	M	3	++	++	1233200000	4	4	4	4	4	4	
13	M	18	+	+	2210000000	0	0	0	4	4	4	

\*Not done.

This small group of tertiary cases is remarkably interesting in several ways. In the first place, there were no clinical symptoms of central nervous system involvement in any of the cases, and hence no special indication for making a lumbar puncture. None the less, the Wassermann reaction was strongly positive in two cases, pleocytosis was found in two fluids, globulin tests were either + or ++ in all, and typical "luetie zone" colloidal gold reactions were obtained with five of the fluids. The blood Wassermann was positive in all five of the specimens examined. Whatever else these findings may indicate, they furnish strong proof of the wisdom of examining periodically the spinal fluid of every individual known to have had lues.

TABLE V.—CONGENITAL LUES.

Case Number.	Ward.	Cells per cmm.	Tests for increased Globulin.		Colloidal Gold Reaction.	Wassermann.						Remarks.
			Ross-Jones.	Pandy.		C. S. F.			Blood.			
						An-tigen.			An-tigen.			
						A	B	C	A	B	C	
30	HL	135	+	+	555542100	4	4	4	4	4	4	Juvenile G. P. " "
91	HL	*	*	*	5555542000	4	4	0	4	4	4	
83	G	12	+	+	1255532100	4	4	4	4	4	4	
144	HL	*	0	0	0000000000	0	0	0	4	4	4	
116	HL	*	0	0	0000000000	0	0	0	4	4	4	
124	HL	*	0	0	0000000000	0	0	0	0	0	0	
258	HL	13	*	*	3333100000	1	1	1	4	4	4	
48	HL	6	0	0	0000000000	0	0	0	4	4	4	

\*Not done.

The results in this series of eight cases of congenital lues are wholly confirmatory of the conclusion reached by Miller and Levy, which was to the effect that the gold reaction "has no advantage over known laboratory methods in the diagnosis of



congenital lues." Leaving out of consideration the first two cases, which were classical examples of juvenile paresis, it will be seen that four of the remaining fluids gave absolutely no reaction with colloidal gold; the two fluids that did react also gave either complete or partial complement fixation. On the other hand, the sera of seven out of the eight cases gave complete fixation, some of them in minimal amounts. This high percentage of positive results is wholly in accord with those published by a number of observers. To quote Boas, whose review of the literature is most comprehensive—"A positive Wassermann is constant in manifest cases of congenital lues both in the first and also in later years. Moreover, as judged by quantitative titrations, the reaction appears to be stronger in congenital syphilis than in all other forms of the disease." The constant verification of this statement constitutes the main evidence for reasserting the superiority of the Wassermann reaction over Lange's colloidal gold test in the diagnosis of congenital lues. The contradictory opinion, again recently advanced by Grulee and Moody, is based, we believe, upon insufficient and erroneous data: insufficient, because of the fact that "the Wassermann reaction, when tested, was made on the cerebrospinal fluid"; erroneous, by reason of their tendency to ascribe diagnostic value to reactions regarded, by almost all observers who have worked with colloidal gold, as entirely too slight to possess any pathological significance. This perhaps may be partly accounted for by the fact that Grulee and Moody have employed solutions showing "a tinge of purple," whereas others have consistently thrown away all such by reason of their known tendency to give false positive reactions.

TABLE VI.—TUBERCULOUS MENINGITIS.

Case Number.	Ward.	Cells per cmm.	Tests for increased Globulin.		Colloidal Gold Reaction.	Wassermann.						Remarks.
			Ross-Jones.	Pandy.		C. S. F. Blood.						
						An-tigen.			An-tigen.			
						A	B	C	A	B	C	
74	M	500	++	++	3333444420	0	0	0	0	0	0	
107	W1	970	++	++	2222234430	4	4	4	0	0	0	
131	HL	*	++	++	2355555550	0	0	0	0	0	0	
254	OS	*	++	++	00233332220	0	0	0	0	0	0	
289	M	250	++++	++++	555555555430	3	0	0	0	0	0	

\*Not done.

Attention is merely called to the fact that in all five of the cases of tuberculous meningitis, typical "Verschiebung nach oben" occurred, more marked in some instances than others. This feature, diagnostic apparently of meningitis of non-luetic origin, is not apt to become pronounced until the condition is well advanced and the clinical diagnosis safely established. In fact, observations recorded elsewhere indicate that, in a general way, the "Verschiebung" runs roughly parallel with the course of the disease. At any rate, the gold curves given by spinal fluids from early cases of tuberculous meningitis are frequently of the "luetie type" and, therefore, may be quite misleading unless repeated punctures are practised. When this is done, one can readily note the gradual transition into the meningitic reaction type.

TABLE VII.—MISCELLANEOUS GROUP.

Case Number.	Ward.	Cells per cmm.	Tests for increased Globulin.		Colloidal Gold Reaction.	Wassermann.									Remarks.
			Ross-Jones.	Pandy.		C. S. F.			Blood.						
						An-tigen.	A	B	C	An-tigen.	A	B	C		
84	C3	120	+++		3+3+3+4554200	0	0	0	0	0	0	0	0	0	Brain tumor.
130	W2	348	+++	+++	4455555430	0	0	0	0	0	0	0	0	0	Brain abscess.
134	W3	125	+	+++	5555555420	0	0	0	0	0	0	0	0	0	Brain tumor, or G. P.
153	W3	264	++	+++	3334433200	0	0	0	0	0	0	0	0	0	Brain abscess.
234	D	1	0	0	0000000000	0	0	0	0	0	0	0	0	0	Brain tumor.
274	E2	*	+	+	0000000000	0	0	0	0	0	0	0	0	0	Brain abscess.
279	W3	3	+	+	0000000000	0	0	0	0	0	0	0	0	0	Brain tumor.
272	M	0	++	++	0000000000	0	0	0	4	4	4	4	4	4	Chronic nephritis.
16	M	82	+	+	122+1000000	0	0	0	4	4	4	4	4	4	Hemiplegia (luetic) ?
45	F	3	+	+	0000000000	0	0	0	4	4	4	4	4	4	Syphilis of cent. nerv. system (?).
58	E	*	±	+	2233321000	0	0	0	0	0	0	0	0	0	Hemiplegia.
129	OS	3	0	0	0000000000	0	0	0	0	0	0	0	0	0	Nonoplegia.
154	F	2	0	0	0000000000	0	0	0	0	0	0	0	0	0	Hemiplegia.
240	CS	3	0	0	0000000000	0	0	0	0	0	0	0	0	0	Hemiplegia.
4	E3	0	0	0	0000000000	0	0	0	0	0	0	0	0	0	Infective exhaustive psychosis.
8	W2	178	+	0	0000000000	0	0	0	0	0	0	0	0	0	Unclassified.
12	E3	6	0	0	0000000000	0	0	0	0	0	0	0	0	0	Hysteria.
15	E1	6	0	0	0000000000	0	0	0	0	0	0	0	0	0	Alzheimer's Disease.
24	E1	4	0	0	0000000000	0	0	0	0	0	0	0	0	0	Hallucinoses.
27	E3	7	0	0	0000000000	0	0	0	0	0	0	0	0	0	Hysteria.
29	E1	3	±	±	0000000000	0	0	0	0	0	0	0	0	0	Cerebral arteriosclerosis.
34	F	*	0	0	1210000000	0	0	0	0	0	0	0	0	0	Parkinson's Disease.
35	C4	3	0	0	0000000000	0	0	0	0	0	0	0	0	0	Myelitis
36	E1	3	0	0	0000000000	0	0	0	0	0	0	0	0	0	Hysteria.
40	C3	5	+	+	0000000000	0	0	0	0	0	0	0	0	0	Cerebral arteriosclerosis.
44	F	5	0	0	0000000000	0	0	0	0	0	0	0	0	0	Myoclonia multiplex.
47	C3	3	0	0	0000000000	0	0	0	0	0	0	0	0	0	Alcoholic neuritis.
49	E	5	0	0	1121000000	0	0	0	0	0	0	0	0	0	Psychoneurosis.
51	C2	5	0	0	0000000000	0	0	0	0	0	0	0	0	0	Trifacial neuralgia.
52	W2	3	0	0	0000000000	0	0	0	4	4	4	4	4	4	Dementia præcox.
65	F	8	0	0	0000000000	0	0	0	0	0	0	0	0	0	Traumatic neurosis.
68	C4	3	0	0	0000000000	0	0	0	0	0	0	0	0	0	Dilated aorta.
69	C4	4	0	0	22+33+321000	0	0	0	0	0	0	0	0	0	Neurasthenia.
70	M	2	0	0	2233100000	0	0	0	4	4	4	4	4	4	Ménière's Disease.
71	E2	2	0	0	1232100000	0	0	0	0	0	0	0	0	0	Unclassified.
81	HL	7	±	±	2233410000	0	0	0	0	0	0	0	0	0	Poliomyelitis.
85	F	2	0	0	3354100000	0	0	0	4	4	4	4	4	4	Nephritis (luetic?).
92	C2	6	0	0	0000000000	0	0	0	0	0	0	0	0	0	Epilepsy.
108	C1	3	0	0	544422100	0	0	0	0	0	0	0	0	0	Multiple sclerosis.
109	E3	7	0	0	1233321000	0	0	0	0	0	0	0	0	0	Hysteria (luetic history).
110	CS	9	0	±	222+3321000	0	0	0	0	0	0	0	0	0	Cerebral arteriosclerosis.
115	DP	1	0	±	0000000000	0	0	0	0	0	0	0	0	0	"
127	F	5	0	0	2233351000	0	0	0	0	0	0	0	0	0	Chorea.
133	C	*	0	0	2233+432100	0	0	0	0	0	0	0	0	0	Diabetes mellitus (acidosis)
137	F	3	0	0	2344+554200	0	0	0	4	4	4	4	4	4	Aneurism.*
142	W3	5	0	+	0000000000	0	0	0	0	0	0	0	0	0	Psychoneurosis.
145	E	*	±	0	1134332100	0	0	0	0	0	0	0	0	0	Arteriosclerosis (cerebral).
148	E2	0	0	0	0000000000	0	0	0	0	0	0	0	0	0	Dementia præcox.
149	E2	6	0	0	0000000000	0	0	0	0	0	0	0	0	0	Unclassified.
157	C1	3	0	0	0000000000	0	0	0	0	0	0	0	0	0	Vertigo.
180	C3	*	+	+	1234321000	0	0	0	4	4	4	4	4	4	Complete deafness.
189	C1	4	0	0	0000000000	0	0	0	0	0	0	0	0	0	Epilepsy.
217	W3	2	0	0	0000000000	0	0	0	0	0	0	0	0	0	Constitutional inferiority.
222	E	2	0	0	0000000000	0	0	0	0	0	0	0	0	0	T. B. of spine.
224	F	1	±	0	0000000000	0	0	0	0	0	0	0	0	0	Senile dementia.
229	C1	1	0	0	0000000000	0	0	0	0	0	0	0	0	0	Depression.
236	HL	5	0	0	0000000000	0	0	0	0	0	0	0	0	0	Rigid pupils.
245	M	*	0	0	0000000000	0	0	0	0	0	0	0	0	0	Anemia.
247	W3	1	±	±	0000000000	0	0	0	0	0	0	0	0	0	Father of No. 173.
256	E3	3	0	0	0000000000	0	0	0	4	4	4	4	4	4	Psychoneurosis.
275	C1	2	0	0	0000000000	0	0	0	0	0	0	0	0	0	"
277	C4	2	0	0	0000000000	0	0	0	0	0	0	0	0	0	Osteo-arthritis.
282	F	*	±	+	4554210000	0	0	0	0	0	0	0	0	0	Cirrhosis of liver.
286	M	1	+	+	2223322100	0	0	0	?	?	?	?	?	?	Hematuria.
299	W1	1	0	0	0000000000	0	0	0	0	0	0	0	0	0	Depression.
309	W1	1	0	0	0000000000	0	0	0	0	0	0	0	0	0	Psychoneurosis.
310	C1	1	0	0	0000000000	0	0	0	0	0	0	0	0	0	Reflexes+, A. R. pupils.
314	W1	0	0	0	0000000000	0	0	0	0	0	0	0	0	0	Pellagra.
319	C1	3	0	0	0000000000	0	0	0	0	0	0	0	0	0	Psychoneurosis.
321	F	6	+	+	0000000000	0	0	0	0	0	0	0	0	0	Neurasthenia.
322	F	4	+	+	2223+220000	0	0	0	0	0	0	0	0	0	Arteriosclerosis (cerebral).
323	F	6	0	+	3333330000	0	0	0	*	*	*	*	*	*	Chronic nephritis.
S	W2	3	0	0	0000000000	0	0	0	0	0	0	0	0	0	Psychoneurosis.
JSP	W4	4	0	0	0000000000	0	0	0	0	0	0	0	0	0	Infective exhaustive psychoses.
EAN	W2	3	0	0	0000000000	0	0	0	0	0	0	0	0	0	Constitutional inferiority.
TES	W3	0	0	0	0000000000	0	0	0	0	0	0	0	0	0	Manic-depressive.
DK	W1	0	0	0	0000000000	0	0	0	0	0	0	0	0	0	Cerebral arteriosclerosis.
CT	W1	1	0	0	0000000000	0	0	0	0	0	0	0	0	0	Paranoia.
CS	W3	6	0	0	0000000000	0	0	0	0	0	0	0	0	0	Hysteria.
WRC	W4	3	0	0	0000000000	0	0	0	0	0	0	0	0	0	Pellagra.
WFP	W1	2	0	0	0000000000	0	0	0	0	0	0	0	0	0	Traumatic psychosis.
ED	CS	5	0	0	0000000000	0	0	0	0	0	0	0	0	0	Cerebral arteriosclerosis.
PRC	CS	4	0	0	0000000000	0	0	0	0	0	0	0	0	0	Tumor of spinal cord (?).
91	C1	28	0	0	0000000000	0	0	0	0	0	0	0	0	0	Dementia præcox.
328	C3	2	+	0	0000000000	0	0	0	0	0	0	0	0	0	Epilepsy.
335	F	0	0	0	0000000000	0	0	0	0	0	0	0	0	0	Hemiplegia (brain tumor).
337	F	6	0	0	0000000000	0	0	0	0	0	0	0	0	0	Aneurism.
334	E1	2	+	+	0000000000	0	0	0	4	4	4	4	4	4	Morphine habitué.
355	W1	4	±	±	0000000000	0	0	0	0	0	0	0	0	0	Traumatic psychosis.
356	M	22	+	+	2222110000	9	0	0	0	0	0	0	0	0	Hypophysis tumor.
357	W2	1	0	0	0000000000	0	0	0	0	0	0	0	0	0	Traumatic psychosis.
359	W2	2	0	±	1112200000	0	0	0	0	0	0	0	0	0	Psychoneurosis.



TABLE VII.—MISCELLANEOUS GROUP— <i>Continued.</i>														
Case Number.	Ward.	Cells per cmm.	Tests for increased Globulin.		Colloidal Gold Reaction.	Wassermann.						Remarks.		
			Ross-Jones.	Pandy.		C. S. F.			Blood.					
						An-tigen.	A	B	C	An-tigen.	A		B	C
363	F	0	+	0	0000000000	0	0	0	0	0	0	0	Myelitis.	
364	F	0	0	0	1122211000	0	0	0	0	0	0	0	Epilepsy.	
371	F	3	0	0	0000000000	0	0	0	4	3	2		Syphilophobia.	
373	W4	1	0	0	0000000000	0	0	0	0	0	0	0	Hysteria.	
376	C3	1	0	0	0000000000	0	0	0	0	0	0	0	Spastic paraplegia.	
377	C1	1	0	0	2211100000	0	0	0	0	0	0	0	Paralysis agitans.	
378	CS	2	0	0	0000000000	0	0	0	0	0	0	0	Chronic alcoholism.	
380	F	5	0	0	0000000000	0	0	0	0	0	0	0	Syphilophobia.	
381	G	2	0	0	2222111000	0	0	0	0	0	0	0	Brain tumor.	
67	W4	2	0	0	2232100000	0	0	0	0	0	0	0	Alcoholic paranoia.	

The Wassermann reaction was negative in all of the 102 spinal fluids included in the miscellaneous group. It was positive in the blood in 11 cases. The colloidal gold test was absolutely negative in 71 instances, and showed various types of reactions in the remaining 31. Of these, five had a positive blood Wassermann. The majority of these gold reactions occurring in the spinal fluids from non-luetic cases may probably be accounted for by the existence of various pathological conditions in the central nervous system. The following tabulation emphasizes this point:

	No. of Cases.
Brain tumor or abscess.....	6
Hemiplegia . . . . .	2
Paralysis agitans . . . . .	2
Epilepsy . . . . .	1
Chorea . . . . .	1
Poliomyelitis . . . . .	1
Multiple sclerosis . . . . .	1
Cerebral arteriosclerosis . . . . .	3
Diabetic acidosis . . . . .	1
Chronic nephritis with acidosis.....	1

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The reactions observed in such conditions as hepatic cirrhosis, idiopathic hematuria, neurasthenia, hysteria and different types of psychoneuroses, are rather difficult to explain. It is our belief, however, that these most probably represent errors in technique rather than the existence of abnormalities in spinal fluids which were otherwise negative.

Multiple sclerosis is deserving of special attention. The one case included in this series<sup>1</sup> (No. 108) gave an extremely strong reaction which was highly suggestive of paresis (5444422100), and was reported as such, much to the surprise and doubt of the patient's physician. That such reactions are by no means uncommon is evident from a study of the literature. Out of eight cases observed by Flesch, "six showed reaction curves which might remind one of paresis, only the curves are usually shorter than those of the latter disease. This type of curve in a fluid otherwise entirely negative may prove of value." Eskuchen records entirely negative findings in three cases of multiple sclerosis and is inclined to doubt the reliability of the paretic curve obtained by Kaplan in one instance. In his most recent article, Kaplan records negative gold reactions in 17 cases of disseminated sclerosis, and a pseudo-paretic curve in one. This question is deserving of further careful study, particularly by reason of the fact that spinal fluids from cases of multiple sclerosis not infrequently show a moderate pleocytosis, positive globulin reactions and occasionally a positive Wassermann reaction, provided large amounts of fluid (1 cc.) are used. Such findings have been recorded by Eichelberg and Kaplan.

<sup>1</sup> Since the above was sent to press, two more classical cases of multiple sclerosis have come under observation: each gave a true "paretic reaction" and negative Wassermann tests.

TABLE VIII.																																													
Author.	PARESIS.											TABES DORSALIS.											CEREBROSPINAL LUES.											MISCELLANEOUS GROUP.											
	Wassermann reaction.											Wassermann reaction.											Wassermann reaction.											Wassermann reaction.											
	Blood.					Cerebrospinal fluid.						Blood.					Cerebrospinal fluid.						Blood.						Cerebrospinal fluid.					Blood.						Cerebrospinal fluid.					
	Number of cases.	Positive.	Negative.	Positive.	Negative.	Pleocytosis.	Positive globulin tests.	Colloidal gold.	Paretic curve.	Luetic zone.	Negative.	Number of cases.	Positive.	Negative.	Positive.	Negative.	Pleocytosis.	Positive globulin tests.	Colloidal gold.	Paretic curve.	Luetic zone.	Negative.	Number of cases.	Positive.	Negative.	Positive.	Negative.	Pleocytosis.	Positive globulin tests.	Colloidal gold.	Paretic curve.	Luetic zone.	Negative.	Number of cases.	Positive.	Negative.	Positive.	Negative.	Pleocytosis.	Positive globulin tests.	Colloidal gold.	Paretic curve.	Luetic zone.	Negative.	
Weston, Darling and Newcomb.	34	31	3	32	2	16	32	31	1	2	0	...	...	...	...	...	...	...	...	...	...	...	3	3	0	3	0	0	3	3	0	0	161	8	153	0	161	1	5	2	8	151			
Lee and Hinton .....	12	8	4	10	2	10	9	11	...	1	24	4	20	11	13	14	7	...	24	...	15	7	8	9	6	12	11	...	14	...	49	8	41	1	48	11	10	...	14	35					
Eskuchen .....	21	21	0	19	2	21	21	7	14	0	33	13	20	8	25	22	20	0	30	3	13	10	3	6	7	8	11	0	13	0	56	12	44	0	56	5	9	0	3	50					
Swalm and Mann .....	70	66	4	65	5	69	66	66	3	1	4	1	3	1	3	3	1	0	2	2	10	10	0	4	6	8	6	0	6	4	27	16	11	0	27	8	8	0	1	26					
Flesch .....	4	...	...	...	...	...	...	4	...	...	23	...	...	...	...	...	...	9	4	...	...	...	...	...	...	...	...	...	...	...	38	...	...	...	...	...	...	...	...	33					
Solomon and Koefod .....	16	16	0	16	0	16	16	14	2	0	12	12	0	12	0	12	0	10	2	9	9	0	9	0	7	8	6	3	0	86	30	56	5	51	0	13	1	10	75						
Kaplan .....	52	49	3	47	5	52	41	48	4	0	125	67	58	43	82	107	34	1	53	71	50	42	8	34	16	49	31	1	15	34	914	0	914	0	914	0	12	1	0	913					
Eicke .....	52	50	2	50	2	50	50	50	0	2	24	22	2	22	2	22	22	0	22	2	25	24	1	24	1	24	24	0	24	1	222	...	...	4	218	104	104	0	68	123					
Crinis and Frank .....	83	...	...	58	25	53	70	83	0	0	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...				
Jaeger .....	33	29	4	29	4	31	31	33	0	0	12	8	4	8	4	11	11	6	0	0	5	2	1	2	4	0	0	0	0	56	...	...	...	...	...	...	5	29	22						
Miller and Levy .....	49	39	10	47	2	43	49	49	0	0	10	0	4	7	3	5	7	0	10	0	15	12	3	8	7	8	12	0	13	2	97	25	72	7	90	0	0	0	43	54					
Miller, Brush, Hammers and Felton .....	130	114	10	121	3	93	116	122	1	1	33	15	13	22	11	20	31	5	24	1	15	11	4	7	8	0	13	4	9	2	102	11	90	0	102	9	33	1	28	73					
Totals .....	556	423	40	494	52	454	501	518	25	7	301	148	124	134	143	206	145	12	190	98	161	130	31	106	55	128	125	20	97	44	1808	110	1381	17	1667	139	194	10	204	1555					



A compilation of the results of a number of authors previously referred to is given in Table VIII. The omissions are due to the lack of sufficient specific information regarding the various reactions designated in the separate columns. It should be pointed out that of the positive reactions included in any of the miscellaneous groups, 48 were given by cases of meningitis, two by cases of multiple sclerosis and 68 by cases of secondary or tertiary lues. Two of the ten "paretic curves" included in the miscellaneous group were given by the cases of multiple sclerosis already referred to, while the five recorded by Jaeger should be thrown out on the ground of faulty technique.

V. A COMPARISON OF THE COLLOIDAL GOLD AND WASSERMANN REACTIONS.

It is well recognized that Wassermann's complement fixation test is a relatively complex procedure, and that consistently reliable results can be obtained only by those specially trained in serological technique. For this reason numerous attempts have been made to perfect tests equally valuable for the diagnosis of syphilis, but at the same time simple enough for more general use. Lange first endeavored to distinguish luetic from non-luetic sera by the colloidal gold reaction, but without success. With spinal fluids, however, he and subsequent observers noted a certain suggestive parallelism between the type of gold curve and a positive Wassermann reaction in cases clinically luetic. Up to the present time no one has made any serious effort to ascertain just what the relationship, if there be one, really is. Eskuchen could formulate no regular rule. He observed fairly numerous unexpected exceptions to the general law that when a strong precipitation of gold

TABLE IX.

Showing the incidence and intensity of the Gold Reactions given by Spinal Fluids in which the Wassermann test was 100% positive.

Clinical Diagnosis.	No. of fluids examined.	No. with positive Wassermann.	Percent of positive spinal fluids.	Maximum color change in gold test.						
				5	4	3	2	1	0	Totals.
Paresis.....	130	123	94.6%	120	2	1	0	0	0	123
Tabes.....	33	18	54.5%	*6	8	3	1	0	0	18
C.-S. lues.....	15	†	40. %	†3	2	1	0	0	0	6
Congenital lues	8	3	37.5%	†3	0	0	0	0	0	3
Tertiary lues...	6	2	33.3%	0	0	1	1	0	0	2
Miscellaneous..	102	0	0	..	..	..	..	..	..	..
Totals .....	294	152	.....	132	12	6	2	0	0	152

\* Three Tabo-Paretics.      †All possible Paretics.      ‡ Two Juvenile Paretics.

occurs in the first four to six tubes, complement fixation is complete even when minimal amounts of spinal fluid are used. Lee and Hinton are of the opinion that the gold test is much more delicate than the spinal fluid Wassermann reaction, and for the same reason not a few have expressed their belief that reactions typical in the "luetic zone" confirm the clinical suspicions of central nervous system lues, even though the Wassermann is repeatedly negative; moreover, such reactions may foreshadow the outbreak of a latent lues, and may prove quite as valuable as the "Herxheimer provocative salvarsan reaction."

We have endeavored to determine whether there is a sufficient basis of fact to justify any of these assumptions, and particularly to ascertain whether one can safely predict, from the intensity and location of the color changes in a colloidal gold reaction, what the serological findings in the spinal fluid will probably be.

An examination of Table IX reveals some very interesting facts. Of 152 spinal fluids which gave complete fixation, 132, or 86.8%, gave colloidal gold curves in which one or more tubes showed a No. 5 reaction, *i. e.*, complete decolorization. One hundred and twenty of these fluids were from cases of general paresis. The reactions occurring in spinal fluids from this disease fall into four main groups:

- Group I—in which tubes 1-4 show a No. 5 reaction.. 25 cases.
- Group II—in which tubes 1-5 show a No. 5 reaction.. 60 cases.
- Group III—in which tubes 1-6 show a No. 5 reaction.. 25 cases.
- Group IV—in which tubes 1-7 or 1-8 show a No. 5 reaction .....

Over 80% of these paretic spinal fluids gave complete fixation when used in amounts as small as 0.1 cc. Such strong reactions are observed with great constancy whenever five or more tubes are completely decolorized, but are also encountered in fluids belonging to Group I. Of the remaining 12 fluids, nine came from cases that were either tabo-paretics (3), questionable cases of paresis, though diagnosed as cerebral lues (3), or from classical cases of juvenile paresis (3). Of the last named, case No. 83 alone gave a gold curve differing from the common paretic type. Two cases of tabes (Nos. 350 and 358) gave typical paretic curves in the absence of any clinical signs of dementia paralytica, while case No. 79 reached a No. 5 reaction only in the fourth and fifth tubes. Reference to Table IX shows that the remaining 20 "Wassermann-positive" fluids gave their maximum color changes as follows:

- 12 or 7.8% showed a No. 4 reaction in one or more tubes.
- 6 or 3.9% showed a No. 3 reaction in one or more tubes.
- 2 or 1.3% showed a No. 2 reaction in one or more tubes.

In other words, the occurrence of a positive Wassermann becomes progressively less as the gold reaction decreases in intensity. In general, complement fixation is complete, but not, as a rule, with amounts of spinal fluid less than .25 cc., whenever the first three to five tubes show a No. 4 reaction. When no tube in a colloidal gold reaction shows a color change greater than No. 3, the result of the Wassermann is a matter of doubt. Strong, weak or negative fixation tests may occur, the latter predominating, the former occurring only when large amounts of spinal fluid are used.

In the examination of 252 spinal fluids from cases of paresis, tabes dorsalis and cerebrospinal lues, *we have never witnessed the combination of a positive spinal-fluid Wassermann in association with a negative or weak colloidal gold reaction.* There can be no doubt that strong colloidal gold reaction may occur, however, when the spinal-fluid Wassermann is absolutely negative. Thus, in the present series, four cases, clinically paretic (82, 88, 140, 113) gave beautiful typical gold reactions with spinal fluids negative, even when tested in large amounts against all antigens. Fordyce of New York mentions a similar



observation, and others may be found scattered through the literature. It is interesting to note that none of the positive colloidal gold tests occurring in any of the other cases clinically luetic with negative spinal-fluid Wassermann reactions, approach the true paretic type; instead, they show all grades of intensity, and, so far as can be determined, have but one common characteristic, namely, the occurrence of the maximum color change in the "luetie zone."

There seems to be no definite relationship between the colloidal gold relation and the occurrence of a positive blood Wassermann in cases showing a negative cerebrospinal fluid. This point can easily be seen by a reference to the miscellaneous group of cases (Table VII). Eleven cases gave positive blood and negative spinal-fluid Wassermann reactions. In six of these the gold curve was normal. In the remaining six the reactions were as follows:

- 1221000000 Hemiplegia—luetie (?).
- 2233100000 Ménière's disease.
- 1234321000 Deafness (luetie history).
- 2344554200 Aneurysm.
- 3333330000 Chronic nephritis—luetie (?).
- 3354100000 Chronic nephritis—luetie.

Some of these reactions are certainly suggestive of the possible invasion of the central nervous system by a luetic process known to be active elsewhere. Suspicions thus aroused should be confirmed by painstaking clinical observations, frequently repeated over a long period of time. In view of the fact that similar unexplained gold curves may occur in cases certainly not luetic, as judged by all known modern methods, it would seem wise, for the present, to reserve judgment as to the exact significance of "luetie zone" reactions observed in luetics without outspoken central nervous system manifestations.

VI. THE COMPARATIVE VALUE OF THE GOLD TEST AND OTHER SPINAL FLUID REACTIONS.

Throughout the studies of the past two years, careful attention has been given to the comparative value of the colloidal gold and other spinal-fluid reactions. It has been pointed out elsewhere that far too many attempts have been made to demonstrate parallelisms whereby one might argue that if one abnormality was found in a spinal fluid, certain others also would be demonstrable. When one recalls the fact that syphilis of the central nervous system is often diffuse in nature, that the symptoms are protean, and that there are many border-line cases of no certain clinical type, it becomes obvious that any expectation of obtaining infallible and characteristic laboratory findings would be unreasonable. The colloidal gold test offers no exception to the general principles that should govern every laboratory procedure. Its errors, though few, undoubtedly exist; the interpretation of its reactions is safest when combined with the analysis of other laboratory and clinical data. The following observations are based upon the examination of approximately 500 different spinal fluids:

(1) Whenever the colloidal gold reaction is absolutely negative (0000000000) all other reactions are also negative in the vast majority of cases. Out of 115 cases with a negative

gold reaction, nine showed a moderate pleocytosis, and one a cellular increase of 470, all other reactions being normal. Positive globulin tests, usually of a border-line type, occurred eight times; a positive Wassermann, never. In spinal fluids otherwise negative, the occurrence of gold reactions of this type (1111000000) is the equivalent of an absolutely negative finding and should be regarded as such. A colloidal gold reaction of the type 1121000000 is so commonly seen in spinal fluids otherwise normal that it probably possesses no significance, especially in cases clinically not luetic.

(2) There is absolutely no parallelism between the degree of pleocytosis and the strength of the colloidal gold reaction. The most pronounced paretic curves frequently occur with a

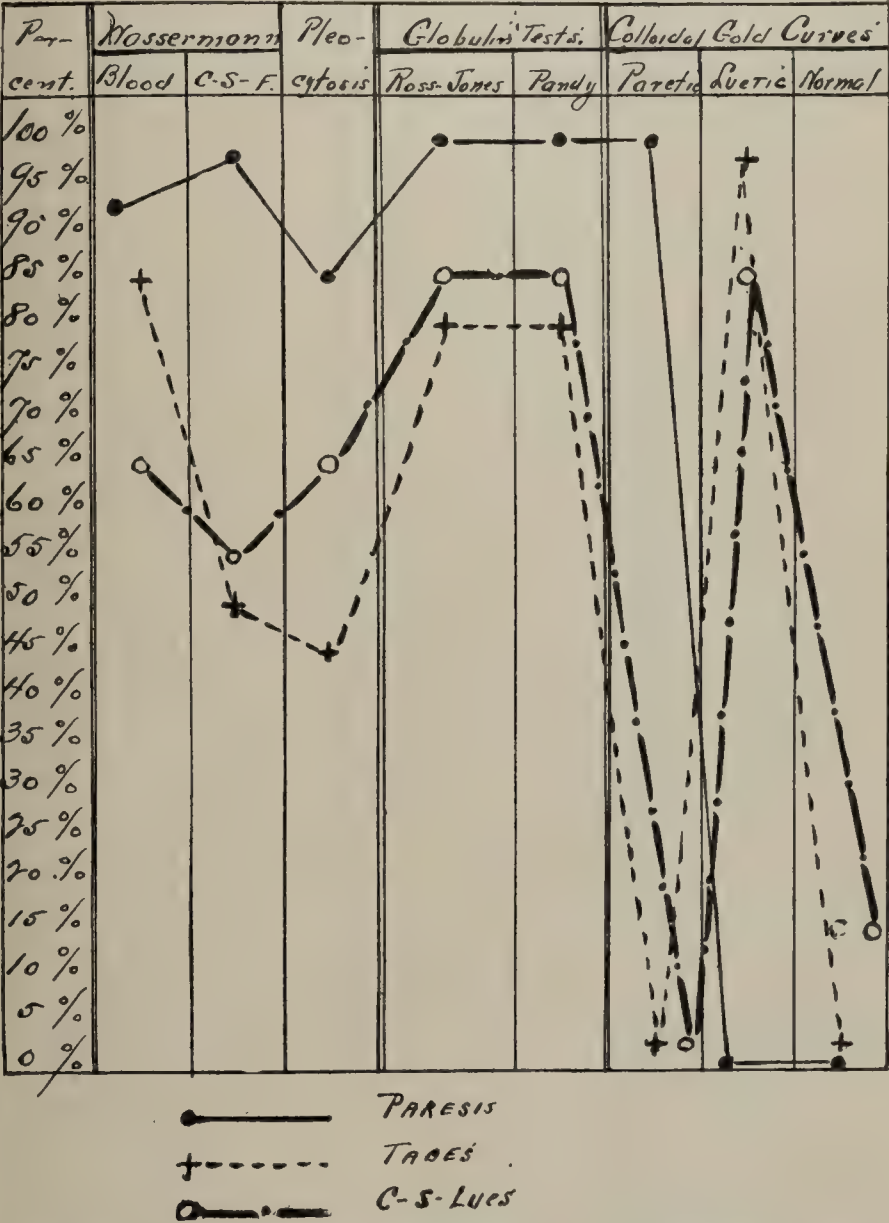


CHART 3.—A graphic representation of the incidence of the “5 Reactions” in Paresis, Tabes and C-S-Lues, based on observations in this clinic.

normal or border-line cell count, while relatively weak gold reactions are not uncommon in association with an outspoken cellular increase.

(3) There is apparently a close relationship between an increased globulin content and positive colloidal gold reactions. No strong color changes in colloidal gold (No. 4 or 5) occur with fluids that give a negative Pandy or Ross-Jones test. On the other hand, positive globulin tests are rarely observed in spinal fluids that give negative or weak gold curves. We have observed a few instances in which globulin reactions were combined with gold curves of the general type (112310000).



The relation to the Wassermann reaction has already been discussed (Sec. V).

In Chart 3 the attempt has been made to present graphically the points which have just been emphasized. In addition, attention is called, in Table X, to the incidence of the various spinal fluid abnormalities in paresis, tabes, and cerebrospinal lues, based upon the observations of Miller and Levy, and those included in the present report. It would appear that diagnostic value can be ascribed not only to the individual abnormal reactions, but also to the total number which may occur in any one case.

TABLE X.

Showing in percentages the frequency with which one or more of the five reactions (Blood W-R, Spinal Fluid W-R, Pleocytosis, Globulin tests and Colloidal Gold Reaction) has occurred in the examination of 500 cases.

Clinical Diagnosis.	All 5 reactions positive.	1 reaction negative.	2 reactions negative.	3 reactions negative.	4 reactions negative.	All reactions negative.	Gold reactions alone positive.
Paresis.....	68	24	6	1	0.5	0	0.5
Tabes dorsalis.....	23.5	32.5	12	17	4	4	7
C-S lues.....	26	24	5	20	16	4	4
Miscellaneous.....	0	1	5	10	14	64	5

VII. SUMMARY AND CONCLUSIONS.

Any further discussion of the general subject presented in this article seems unnecessary by reason of the summary and detailed descriptions to be found in the various sections. In general, it may be said that this study has quite consistently confirmed the conclusions advanced by Miller and Levy in 1914. The results may be epitomized as follows:

(1) In the great majority of cases a normal spinal fluid produces no changes whatever in suitably standardized solutions of colloidal gold. The evidence is strongly in favor of the view that very slight gold reactions, occurring in fluids otherwise normal, probably possess no diagnostic significance. The fact that colloidal solutions in general are unusually sensitive, makes it highly probable that these faint reactions are due to factors which the most scrupulous technique cannot invariably eliminate.

(2) The general reactions observed in tabes and cerebrospinal syphilis are not in themselves characteristic of either condition. As a rule, the curves are typically of the luetic type and are therefore valuable in confirming a doubtful clinical diagnosis, particularly in cases where one or more of the other reactions are negative. It is probably true that the reactions in cerebral lues vary with the type and stage of the disease. Further studies are necessary to determine the exact significance of the paretic curves observed in a few cases showing no clinical evidence of general paralysis.

(3) The reaction type observed in cases of paresis has been so uniformly present and so characteristic as to warrant the following conclusions:

(a) Spinal fluids from *clinical* cases of dementia paralytica cause complete precipitation of colloidal gold in the first

4-8 tubes. Exceptions to this rule have not been observed thus far in this clinic.

(b) The apparent specificity of this paretic reaction is further shown by its occurrence in a number of typical cases in which all other spinal fluid abnormalities were absent. One such case has been confirmed by autopsy.

(c) The fact that a paretic curve *occasionally* occurs in patients who show no evidence of dementia, in no way argues against the value of this reaction. All such reactions have occurred in cases undoubtedly luetic with the exception of a few cases of multiple sclerosis above referred to; none in this series has been followed long enough to make certain the assertion that paresis will not ultimately develop. One must not lose sight of the fact that authentic cases are on record in which, "without the existence of any obvious psychosis, general paralysis was discovered at autopsy." Other patients dying in one of the periods of remission, during which the mentality was relatively high, have shown the well marked and active pathological lesions of paresis; and, in cases of short duration, there is anatomical evidence that the disease had existed long before symptoms attracted attention to it.

(d) The opinion is, therefore, advanced that the occurrence of a paretic reaction in a luetic individual should invariably be looked upon as one of grave portent. For, although paresis may not become outspoken, one at least may be reasonably certain that even prolonged and intensive treatment is not apt to modify the underlying disease to any appreciable degree.

(4) More recent and unpublished work goes to indicate that the substance or substances in the cerebrospinal fluid which induce colloidal gold precipitation are, in part at least, dialysable. It is quite probable that this may ultimately explain reactions simulating a luetic type, which are given by spinal fluids showing no increased globulin content, but obtained from patients who undoubtedly have abnormal changes, either anatomical or functional, in the central nervous system, not necessarily of luetic origin.

(5) Fluids from cases of purulent or tuberculous meningitis give reactions which are usually maximal in the higher dilutions. As a rule, however, careful search will reveal the tubercle bacillus in the spinal fluid before the characteristic "Verschiebung nach oben" develops.

(6) The reactions given by spinal fluids from cases of suspected congenital lues are generally not sufficiently characteristic to warrant a positive diagnosis, and certainly should not be relied upon to the exclusion of other laboratory procedures. The chief exception to this statement is furnished by cases of juvenile paresis.

(7) The colloidal gold reaction does not in any sense replace other cerebrospinal fluid tests of known value. In certain instances it seems to possess a sensitiveness and specificity shared by none of the others. Its sources of error are few and are readily recognized; its results are for the most part clearcut and decisive; its performance requires a minimal amount of spinal fluid, and a technique of extreme simplicity.

(8) The entire value of the reaction is dependent upon the use of a reagent suitably prepared and standardized.



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A CASE OF PULMONARY MONILIASIS<sup>1</sup> IN THE UNITED STATES.<sup>2</sup>

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Pulmonary mycoses referable to groups of organisms more or less well known to American or European observers have in late years been frequently reported, but, so far as the authors are aware, no case in which the causative agent was a *Monilia* has yet appeared in the literature. It therefore seems desirable to make a brief record of this case.

*Past History.*—The patient,<sup>3</sup> a white female, a native American housewife, 44 years of age, was admitted to the City Hospital, Bay View, on January 4, 1915, giving the following history: Prior to her present illness, she had been normally robust; the only sickness of note having been an attack of smallpox at the age of four. She had borne three healthy children and, in addition to her household duties, for fifteen years had worked each summer in canning factories. She gave no history of any previous chronic cough or any other evidence of pulmonary disease.

*Present Illness.*—Early in May, 1915, she applied at a dispensary for treatment on account of what she called a "boil" in the left axilla, which had been present and gradually increased during the three months previous. She had had little or no pain, nor had there been any discharge. On examination a tumor was found in the left breast and the diagnosis of mammary carcinoma with axillary metastases was made. The patient refused operation and soon left the city for her usual summer work in the canneries. During the latter part of the summer she began to notice increasing numbness and tingling in the left hand with some weakness, and a painless swelling of the upper arm. This latter condition continued to increase, so that by early December she was quite incapacitated, the

swelling having by this time extended to the breast and the tissues of the chest wall on this side. There was a gradual development of malaise and feverishness. She was admitted to The Johns Hopkins Hospital, December 26, where the diagnosis of mammary carcinoma was confirmed and a large fluctuating axillary abscess was incised and drained. At this time there was no cough nor expectoration observed. Four days later she was discharged and told to return for dressings. This she was unable to do, and after five days at home she was admitted to the City Hospital. During this interval she had developed a severe cough with profuse expectoration of a red-dish-gray material.

*Physical Examination.*—On admission the patient seemed very ill; her temperature was 102, and she was markedly prostrated. She was breathing somewhat rapidly and coughing at frequent intervals. Her tongue was dry and coated with a whitish fur. The mucous membranes of the mouth were not injected and showed no abnormalities. The teeth were in a poor state of preservation; many of them were missing and those remaining were carious. The pharynx was injected; the tonsils were not enlarged. The thorax was somewhat emaciated; the musculature poorly developed and the subcutaneous fat scarce. The left mammary gland was larger than the right, and in its lower right quadrant there was a hard, irregular mass; this was freely movable over the underlying tissues and the skin was not adherent to it. The nipple was not retracted and not apparently connected with the mass. The remainder of the gland was of a firmer consistency than normal. The right breast was normal. About five centimeters from the left arm on the anterior axillary border there was a sinus-opening about 1.5 cm. in diameter; the sinus tract extended upward and posteriorly for about 4 cm. (Fig. 1). There was a slight sanguineous discharge from it. The infra-clavicular and supra-clavicular fossæ were obliterated by brawny edema of the tissues, which were reddened and hot to the touch. At the summit of the

<sup>1</sup> The term "Moniliasis" is tentative, as representing our present ideas as to the classification of the organism.

<sup>2</sup> Read at a meeting of the Association of American Physicians in Washington, D. C., May 12, 1915.

<sup>3</sup> The patient was admitted to the surgical service of Dr. A. M. Shipley, who kindly permitted us to study and report the case.



supra-clavicular fossa there was an area of softening and fluctuation. The shoulder and upper arm were diffusely swollen and there was some edema and cyanosis of the forearm and hand. There was great loss of power in the left arm, but no paralysis. The left chest showed marked impairment on percussion, especially over the upper lobe, enfeebled breath sounds, prolonged expiration and diminished fremitus. There was well-defined cracked-pot resonance below the clavicle and in the supra-spinous fossa. A localized friction rub was present in the axilla. The right lung seemed normal on percussion and auscultation. The heart was normal. The radial pulse was smaller on the left side. The spleen was not palpable. The abdomen, pelvis and lower extremities showed nothing further of interest.

*Blood.*—Leucocytes 13,000; Hemoglobin, 60% (Sahli); Wassermann, negative. The urine showed no abnormalities.

The *sputum* was very abundant, of a gruel-like character, odorless and faintly tinged with blood. On examination between glass plates, it was found to contain small grayish masses, from 1-2 mm. in diameter; these, when isolated and examined microscopically, showed mycelial threads and yeast-like cells.

*Course of the Malady.*—After three or four days in the hospital the amount of sputum became somewhat diminished and the cough less frequent. The patient was somnolent; the fever persisted. Five days before her death the discharge from the sinus became profuse and the expectoration almost disappeared. Late in the afternoon of this day a severe hemoptysis took place with a simultaneous slight discharge of dark blood from the sinus. After this there was a marked diminution in the cough, but the sinus continued to discharge. The patient's weakness became progressively more marked; and on January 17, after a profuse hemorrhage from the sinus, without any hemoptysis, she sank and died in a few moments.

*Autopsy.*—At the autopsy, which was performed three hours after death, the sinus tract was found to arise from two large abscess cavities, which lay respectively above and below the clavicle in the upward continuation of the axillary fossa. These inter-communicating cavities still contained a considerable amount of purulent material of a reddish-brown tinge. Where these cavities were bounded by the thoracic wall, there was evidence that at numerous small points they communicated through the intercostal spaces with the inside of the chest. The intercostal muscles were infiltrated, edematous and friable. Upon pressure on the chest there appeared at many points, in the intercostal spaces affected, a trickling of the bloody discharge mixed with bubbles of air coming outward through the musculature, but at no point was a large single communication through the chest wall discovered.

The left breast contained several large nodular masses of firm consistency, which on section were grayish and translucent on the cut surface, but also showed yellowish granular areas.

The left thoracic wall was disarticulated at the sterno-clavicular notch and the entire chest wall including the lung was peeled out of the skin.

The examination of the left lung and chest wall showed the lung to be bound by dense fibrinous adhesions to the parietal pleura in the upper and posterior third. Particularly at the apex these adhesions were very dense and almost cartilaginous in consistency; in many instances they were 1 cm. in thickness. The remainder of the lung could be lifted from the chest wall, as it was bound only by delicate adhesions. On palpation the greater part of the upper lobe seemed to be densely consolidated and to contain no air.

A section made through the lung, dividing it into two parts from apex to base, revealed a cavity, about 8 cm. in diameter, between the two layers of the pleura and just beneath the apex. This cavity contained a large friable reddish-brown clot. It was surrounded by a fibrinous wall.

The upper lobe of the lung was consolidated, firm in consistency, gray in color, and with a smooth surface. The remainder of the lung showed areas of similar consolidation, growing sparser towards the base, where only a small proportion of the lung was actually involved.

The bronchi, particularly those leading to the upper lobe contained a reddish-brown coagulum that was quite friable, and in some areas was laminated. The blood-vessels showed no marked abnormality. The glands at the hilus of the lung and in the mediastinum were enlarged and firmer than normal in consistence. On section they showed pigmentation and the presence of translucent grayish areas of infiltration.

The right pleural cavity and the right lung appeared normal.

Little else of interest was found at the autopsy. The reduction in nutrition was evidenced by the scant subcutaneous fat and the atrophic musculature. There was, in all the tissues, evidence of the acute anemia, secondary to the hemorrhage. The parenchymatous organs showed a moderate degree of cloudy swelling. Nowhere was there any evidence of a metastatic extension of the process localized in the left lung, left pleura and left axillary fossa.

*Microscopical Study of Tissues.*—Sections through the lung show a patchy consolidation which assumes lobar proportions in the upper lobe. The bronchi are everywhere filled with a cell-mass of varying composition, consisting, in part, of pure red blood-cells and in other parts of mixtures of mononuclear cells, of polyblastic type, and of polynuclear cells. The inflammatory cellular mass involves the walls of the bronchi in many places. These are thickened, only partly fibrosed, and contain many polyblastic cells. At other points the bronchial epithelium is well preserved and shows the normal ciliation or a metaplasia into several layers of stratified cubical cells.

The exudate in the alveoli varies considerably. For the most part it is poor in nuclei and is composed of a pink-staining hyaline-like material. This may in places show a filamentous fibrin-like structure; the filaments here and there pass through the pores of Kohn in the alveolar wall. The meshes of this material enclose desquamated cells and small mononuclears; while red blood-cells are uncommon. The alveolar exudate at other points is composed almost wholly of masses of mononuclear and polynuclear cells with little or no fibrin. The alveolar walls are often broken down in these cell-rich areas. The





FIG. 1.—Photograph five days before death. Sinus and infiltration of left thorax and arm.

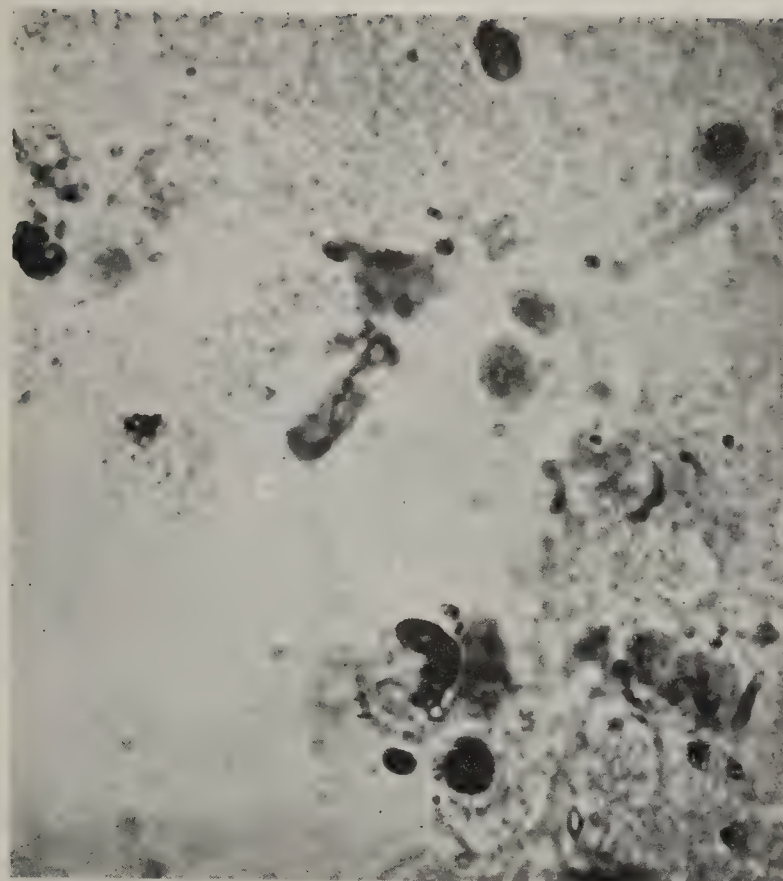


FIG. 2.—Author's case. Section from clot in bronchus. (a) Part of filament with coccoid beading; Victoria blue Weigert stain. ( $\times 1000$ .)

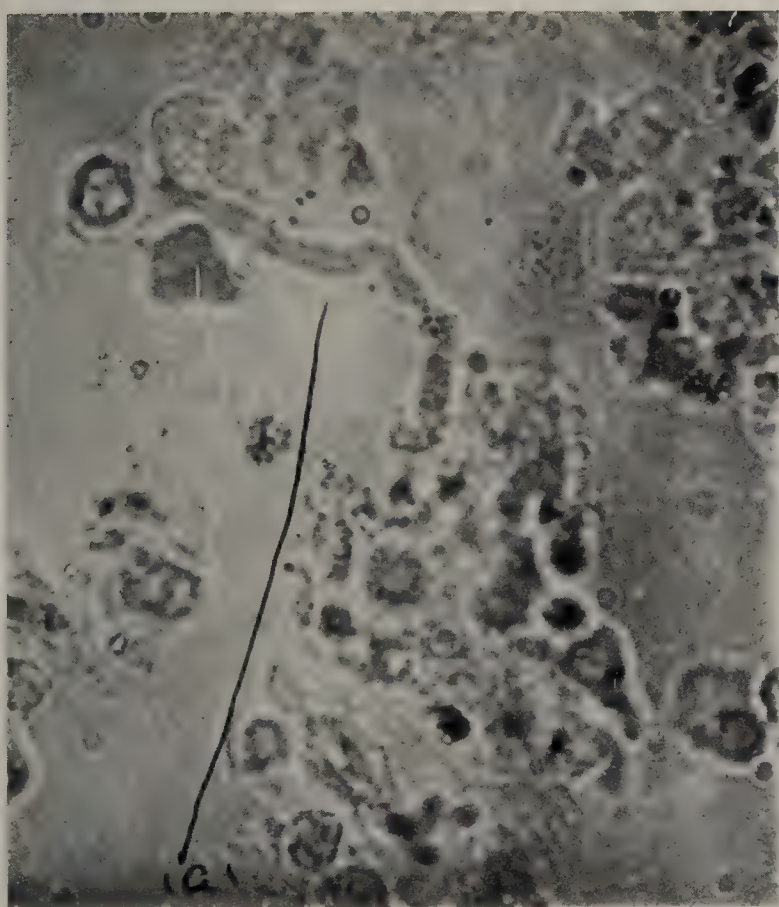


FIG. 3.—Section from pleural exudate. Author's case. Victoria blue Weigert. ( $\times 1000$ .) Showing long cylinder (a) and coccoid forms.



FIG. 5.—Old Culture. Victoria blue. Showing variations in staining. Note coccoid intrahyphal structures (a, a).



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FIG. 7.—*Monilia* (?). Author's case. Section from 8-day gelatin stab, fuchsin stain. Fruiting hyphæ with lateral and terminal sporulation. ( $\times 1000$  diam.)

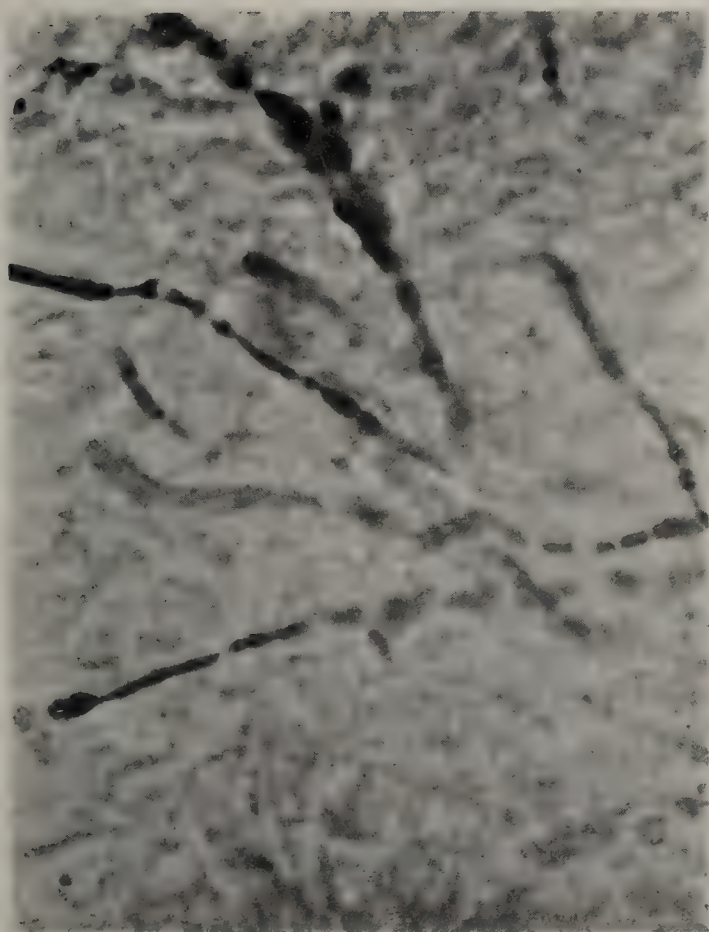


FIG. 4.—Author's organism in kidney of rabbit. ( $\times 1000$ .) Toluidine blue stain. Note similarity to Fig. 3.

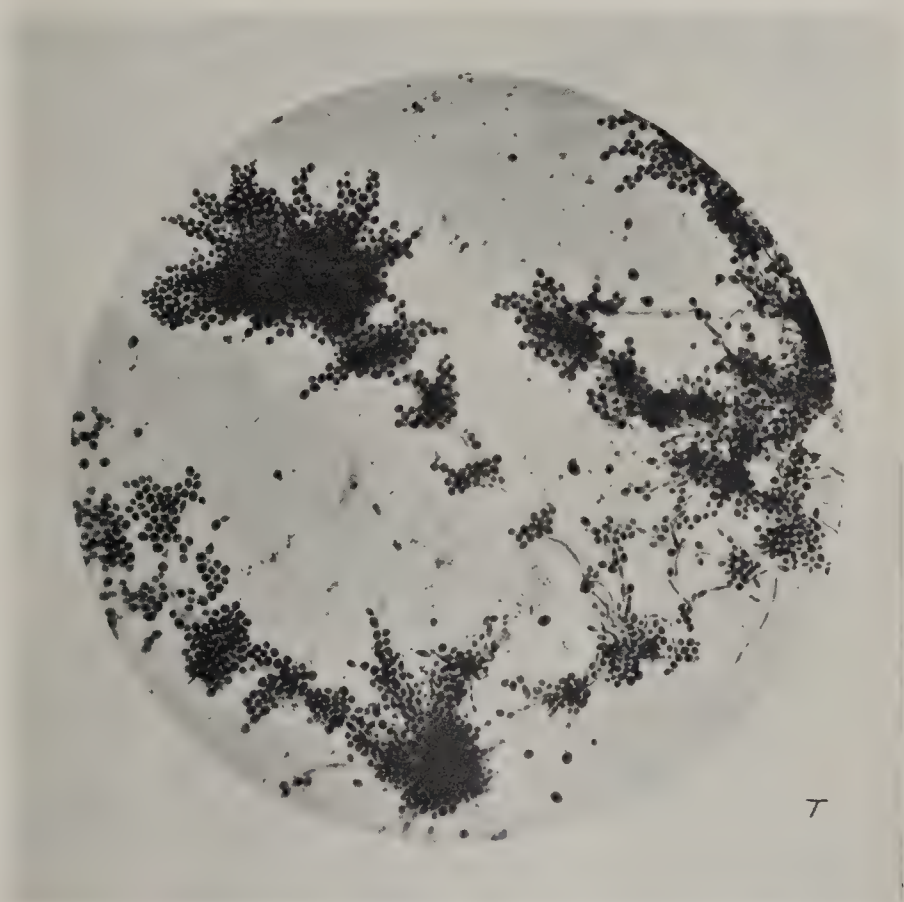


FIG. 9.—*Endomyces albicans* (?). From a child with thrush. Fuchsin stain. ( $\times 500$  diam.) Radial threads and axial spore-clumps.



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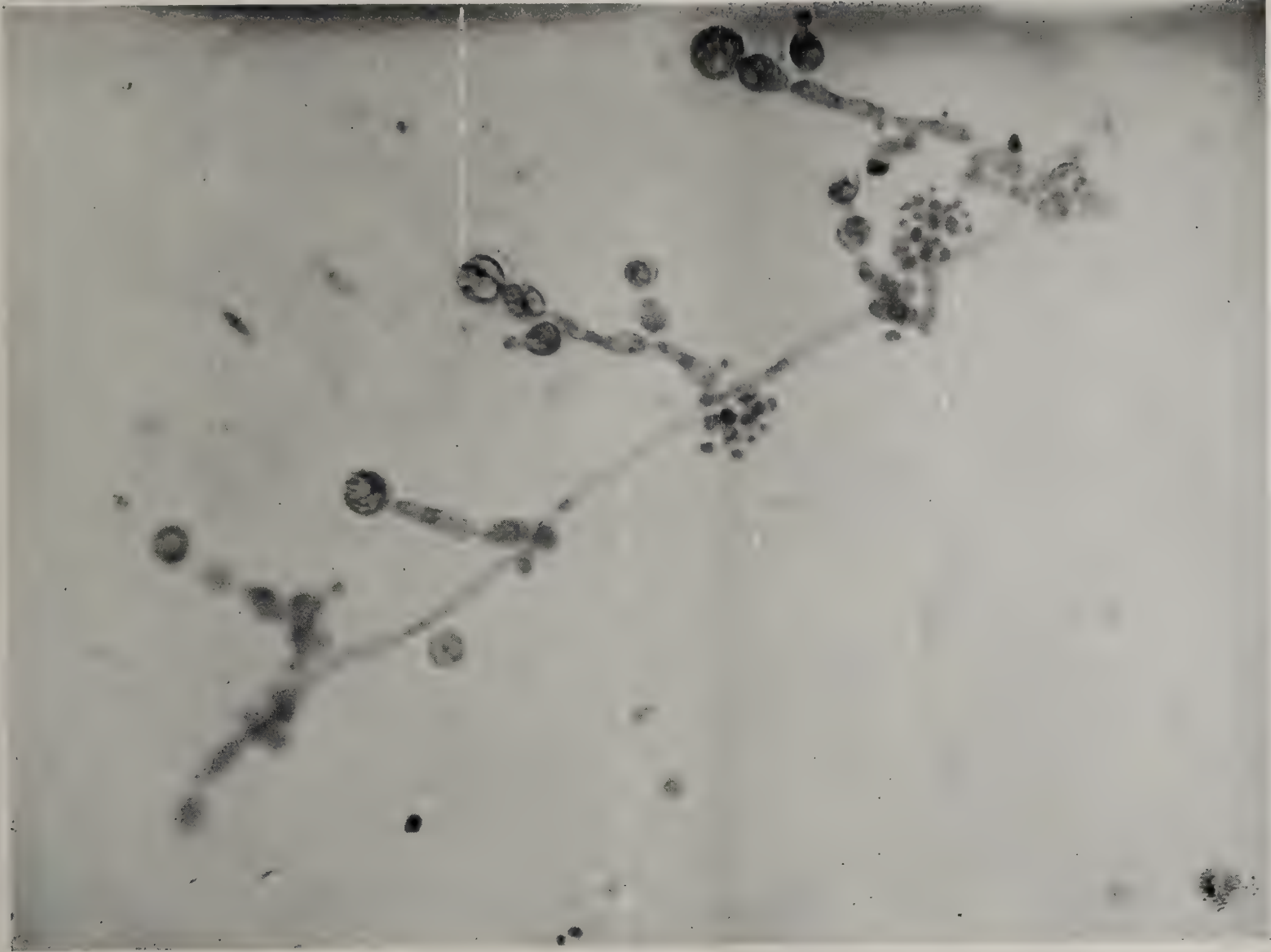


FIG. 8.—*Monilia*(?). Author's case. Section from 8-day gelatin stab, fuchsin stain. ( $\times 1000$  diam.) Hypha (A) with ordinary spores (B) and chlamydospores (C) on same thread.

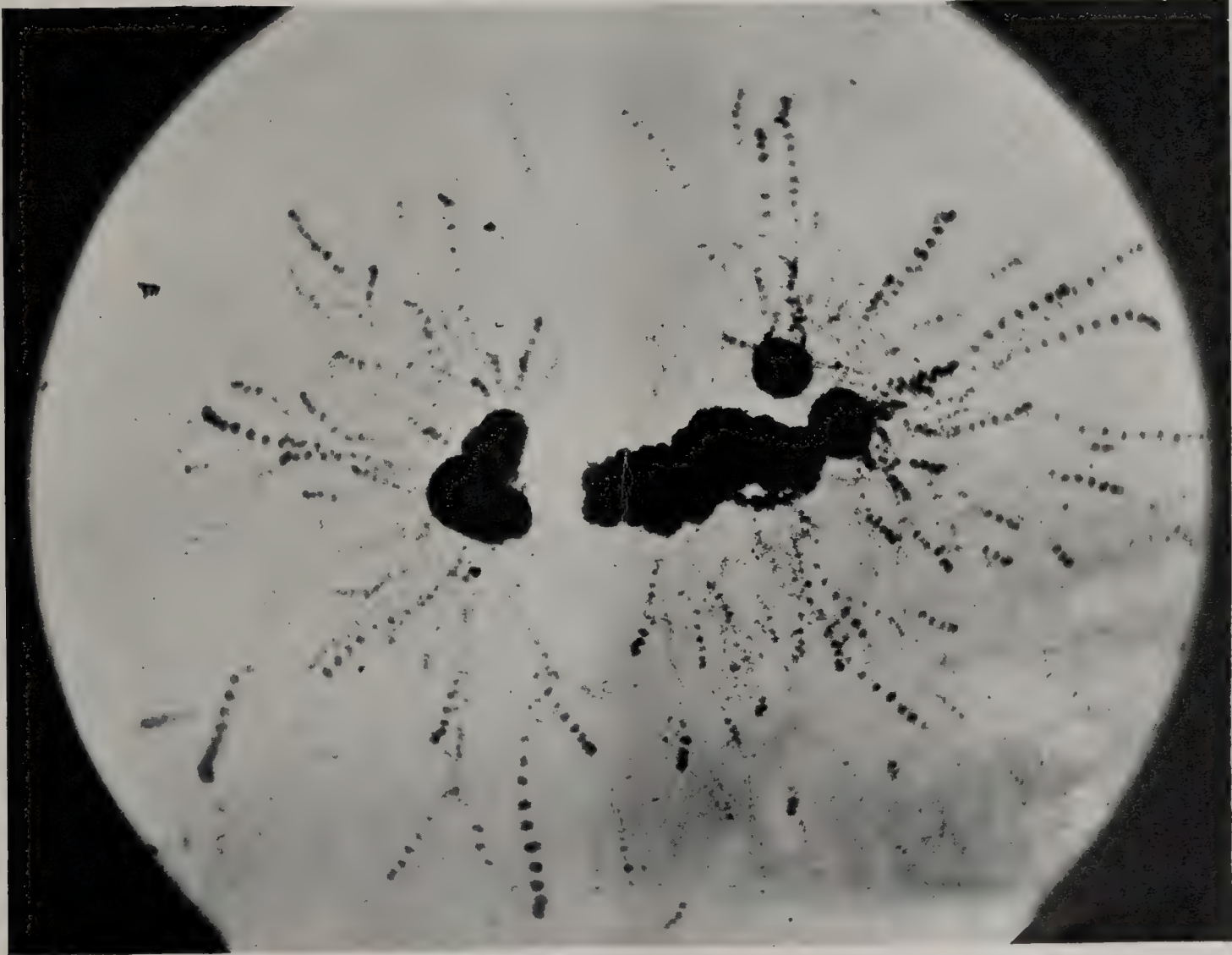


FIG. 6.—*Monilia*(?) Author's case. Section  $\times 80$  diam. Fifteen-day gelatin stab. Victoria blue stain. Radial growth of threads and axial spore-clumps. Dark masses in center composed of spores similar in all respects to the axial spores on threads.



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points of cell-rich exudate grade gradually into the areas in which fibrin-like material predominates.

The pleura is greatly thickened and fibrous. In this inflammatory tissue are found nests of mononuclear and polynuclear cells. This process connects the lung surface with the skeletal muscles, and where the latter are involved, evidence of hyaline and waxy degeneration of the fibres and formation of muscle-spindles is abundant.

By Weigert's method, in the greater part of the alveolar exudate and some of the pleural exudate, single as well as massed filaments stain intensely and resemble fibrin.

The microscopic demonstration of the organism in this tissue has presented great difficulties, as the elements, that we have considered to represent the parasite, decolorize with almost the same readiness as the surrounding tissue.

With the ordinary Weigert stain under the oil-immersion lens, numerous bac' ria-like structures are found occurring as single coccoid forms or in chains. The individual elements, however, are not so uniform in size as cocci, are larger, and the chains formed by them assume much more tortuous and bizarre shapes. A characteristic picture with this stain is the occurrence of these coccoid bodies in double parallel rows. Here and there filaments may be seen connecting the individual beads in the same row or crossing to the opposite side. In other forms the filaments may be more conspicuous and the beads less so.

A modification of the Weigert stain, in which Victoria-blue replaces gentian-violet, seems to give more definite pictures of these bodies and to bring out other related forms which are not seen with the ordinary Weigert stain. These latter occur in masses, appearing sometimes as very long cylinders and sometimes being ovoid; their diameter is about that of a red blood cell; they stain rather deeply blue, and often contain coccoid bodies similar to those described above.

Our impression that the above described elements are mycelial forms of the parasite is strengthened by a comparison with stained specimens of old cultures. We have frequently noted in smears and sections of old cultures that many of the hyphæ are indicated only by faint shadows, others only by a more or less beaded margin, and still others by wavy cylindrical and ovoid forms with or without granules.

*The Left Breast.*—Sections through the indurated lump in the left breast revealed a diffuse carcinoma.

*Cultures from the Sputum.*—The particles from the sputum above-described, which contained mycelium, were washed in sterile salt solution, streaked on plates of media in Petri dishes (potato, bread, agar, glucose-agar) and observed at room temperature, as well as in the thermostat at 37° C. From the potato and glucose-agar plates especially, numerous discrete, whitish, moist, glistening, somewhat waxy colonies, were obtained. On examination these were found to be made up of yeast-like cells, showing active budding, but no hyphal forms. In addition to these colonies there were a few bacterial colonies, scattered among the various plates. The yeast colonies, however, were present in considerable numbers on practically every plate, and on many in pure culture. This method of culture was repeated with similar results a few days later.

The cultural characteristics of this yeast-like organism were studied in various media, and at different temperatures, both aërobically and anaërobically. It was found to grow luxuriantly on glucose-agar with the production of a rather characteristic streak, at first moist, glistening, and opaque, becoming more granular and waxy, with wavy margins and heaped-up center. There was a marked tendency for the dried out portion to take a brilliant white color, suggesting crumbs of chalk. Litmus-glucose-agar was first acidified, becoming slowly alkaline, after from 8 to 10 days. In broth the growth was less abundant, granular, whitish, and always on the bottom, with a clear supernatant fluid and no pellicle. There was a fair growth in milk, without acid production, but after from three to five weeks there developed a late coagulum together with an alkaline reaction. This coagulum was dense and uniform; it resembled soap and stained deeply blue with the alkaline litmus. There was no fluid expressed by this coagulation. Dextrose and lævulose were slowly fermented with a very moderate amount of gas production, which later was almost completely absorbed. There was a slight acid production and only a little alcohol. Saccharose, lactose, and mannite were not fermented. There was no indol-production in meat broth. Gelatine was not liquefied. Stab cultures in agar and gelatine grew freely in opaque, granular, confluent colonies, showing a good growth even at the bottom of deep stabs. Hyphal threads, as noted below, did not appear in early cultures. In anaërobic cultures the production of acid and gas in carbohydrate media was much enfeebled.

#### THE MORPHOLOGY OF THE ORGANISM.

On the surface of solid media aërobic and anaërobic cultures grew as yeast-like forms with active budding, lateral and terminal. Older cultures began to show a few short threads and oïdial chains, but it was not until the strain had been on media for several weeks and repeatedly transferred, that the rapid production of hyphæ and sporulation forms was observed in deep stabs and old fluid cultures. It may be noted also that thread production in all media was more rapid in anaërobic cultures, and when once established it remained constant.

The yeast-like cells varied in size from 2.5 to 7 microns in their longest diameter, the smaller forms being only very slightly refractile, filled with protoplasm and indistinguishable from the spores. The larger showed highly refractile double-contoured walls and were vacuolated, with scanty cytoplasm. The hyphal cells varied from 4 to 8 microns in width and in length from a few microns to several millimeters. They were mostly jointed at irregular intervals, except the sterile hyphæ, which were narrower and often entirely non-septate. No evidence of chromogenesis occurred in any cultures. Smears fixed by heat and stained showed the yeast forms heavily stained without differentiation, whereas the hyphal cells were often barely tinted or entirely unstained. All the forms were Gram-negative.

The threads produced in deep stabs and old fluid media were highly refractile and showed only a small amount of intercellular substance. Small free granules (mitochondria (?)) with



Brownian motion were frequently observed within the hyphæ in fresh preparations. In the surface growth the threads formed were much shorter and, though often jointed, showed little tendency toward branching.

Branching, which is a striking feature in old glucose-bouillon and stab cultures, occurs only at a joint by the budding process. Branching may be simple or compound (Figs. 6 to 9), secondary branches arising, as the primary ones, by budding at the joints. These may show the same phenomena of sporulation as the original hyphæ. Sterile hyphæ are frequent and in the stab cultures may occur in tufts.

The methods of reproduction observed in our cultures were: (1) oïdial chains of spores from large yeast-like cells or hyphæ; (2) lateral masses of free spores without sterygmata (Figs. 6 and 7), which developed by budding at the joints of the hyphæ; (3) terminal sporulation by budding or constriction at the ends of hyphæ. The spores so produced are morphologically like the yeast cells; (4) chlamydospores, which may form at the end of short or long hyphæ, or singly or in groups at the joints of primary or secondary branches. As to the occurrence of sterigmata we saw none unless the structures bearing the chlamydospores in Fig. 8 may be so interpreted. Ascosporeulation has as yet not been found.

These facts bring the organism in close relation to *Monilia candida* (Bonorden), and we have adopted the generic name *Monilia* for our organism as distinguishing it from *Endomyces albicans* which it somewhat resembles (Fig. 9), ascosporeulation being an accepted determining feature of the latter genus. Our *Monilia* is morphologically indistinguishable from that described by Ashford for tropical sprue.

The best pictures of thread production and sporulation were obtained in stab cultures in 15 per cent gelatin, in which the threads grew at right angles to the stab, producing a thick hair-like outgrowth, which occurred at all levels but was best developed just below the surface. The cultures were fixed and hardened in the tube with 10 per cent formalin, the glass was cracked and peeled off, and blocks were cut out at any desired level. The blocks were then sectioned with the freez-

ing microtome. These sections were stained in dilute aqueous fuchsin (1:30), for several hours, and differentiated in saturated aqueous citric acid until the gelatin was nearly decolorized; they were then floated on clean slides, air-dried without blotting, quickly cleared in xylol and mounted in balsam. Full details of this method will be found in our article in the BULLETIN OF THE JOHNS HOPKINS HOSPITAL, 1915. XXVI, p. 354.

These stained sections of stab cultures give a true picture of the actual relation of the threads and spores, as has been described in detail in a previous communication.

#### PATHOGENICITY.

We found the organism actively pathogenic for rabbits, intravenous injection producing disseminated lesions in the kidney cortex, intestinal lymph follicles and liver, as well as in the striped and unstriped muscles; death occurring in one to eight days. Intratracheal injection in rabbits led to localized pneumonia-like lesions in the lungs with pleurisy and late involvement of other viscera. These animals survived, for the most part, several weeks. The organism has been recovered in pure culture from the experimental lesions of rabbits. Sections from these lesions show the organisms in varying abundance and principally in the form of threads (Fig. 4). It is often very difficult to stain the organisms in the tissues, a trait not infrequently observed in mycotic infections. Further studies in the experimental infection of animals are in progress.

We wish especially to acknowledge our indebtedness to Dr. M. C. Winternitz, for his constant assistance in these pathological and experimental studies.

We are also greatly indebted to Dr. W. W. Ford for the facilities furnished for the study of the cultural characteristics of the organism.

Dr. Erwin F. Smith, of the Bureau of Plant Pathology, and Dr. Admon Clark, of The Johns Hopkins University, have most kindly made some of the micro-photographs, which we gratefully acknowledge in this place.

## A MIXED TUMOR (CHONDRO-FIBRO-EPITHELIOMA) OF THE CHOROID PLEXUS.

By W. H. BURMEISTER, M. D.

(From the Department of Pathology of the University of Illinois.)

Tumors of the choroid plexus are usually classed as fibro-epithelial tumors, the epithelial elements predominating. They have, as a rule, a papillary or adenomatous structure. There has been much controversy as to the histogenesis of the epithelial components. Tumors originating from the ependymal lining of the ventricles also generally possess a papillary or adenomatous structure and no doubt some of these are recorded in the literature as growths primary in the choroid plexus.

Two recent reports of papillary tumors of the choroid plexus<sup>1</sup> both contain good reviews of the literature, and in each there are mentioned some observations not included in the review of the other. Natonek makes two main groups: those arising from plexus epithelium and those from the ventricle lining. In most instances there is a marked simulation of the

<sup>1</sup> Slaymaker and Elias, Arch. Int. Med., 1909, iii, 289. Natonek, Virchows Arch., 1914, CCXVIII, 170.



choroid plexus in their structure and many writers have commented on their benignancy and their development as an hyperplasia of the plexus rather than a tumor growth. Macroscopically they are papillary or cauliflower-like and show regions of hemorrhage, lime deposition and necrosis, all no doubt consequences of the difficulties in obtaining nourishment through the slender, tortuous blood-vessels in the branching delicate stalk-like stroma on which the epithelium is spread. Of course, these growths are serious clinically, because of the intracranial pressure they exert; they are, however, not to be reckoned as malignant tumors.

Natonek cites twenty-three choroid-plexus tumors, fourteen of which resemble very much a hyperplasia of the choroid plexus and nine of which are very much unlike the normal choroid plexus in histological structure. To the former should be added five other choroid-plexus tumors cited by Slaymaker and Elias, which are not included in Natonek's review, and to these, again, the tumor described by Sjoevall,<sup>2</sup> a cystic growth of the third ventricle, attached to the choroid plexus in its dorsal portion, the cyst lined with ciliated epithelium, the cells markedly vacuolated and containing lipochrome. A papillary tumor of the third ventricle recently described by Guizzetti,<sup>3</sup> shows a multilayered epithelium of prickle cells and probably originated in the wall of a cyst of the hypophysis. Its epithelial cells bear no resemblance to ependymal cells or choroid-plexus epithelium, and although in its gross structure it appears quite like choroid-plexus papillomata, it should not be classified as one of them.

In the case reported here the tumor was a growth of the choroid plexus in a male negro about 60 years old. Clinically, the man was under observation only two hours before death occurred and during all this time in a semi-comatose condition. Very little could be ascertained regarding his personal history. He had suffered during the previous 6 years from headaches, which would last 4 to 5 days and recur frequently. Four years before death he fell unconscious on the street and remained so 24 hours. He was bedridden for a week after this, and then gradually resumed his duties as a porter in a saloon. Two days before death he fell, striking his head, and remained semiconscious. For at least a month previous to this he had complained of a continuous frontal headache, dull, constant, and always worse at night. In the hospital, where he lived only 2 hours, his temperature was 98, pulse 80, respirations 20, systolic blood pressure 118. Three spinal punctures all showed large numbers of intact erythrocytes. Physical examination of the trunk disclosed nothing noteworthy; the urine was negative. There was no rigidity of the neck; the jaw was firmly closed; the tongue did not deviate. The left pupil was contracted to pin-point size, the right measured 2 mm. in diameter; neither reacted to light. There was an external lateral strabismus of the right eye. The ears and nose were negative. Both forearms were flexed; the left arm was spastic.

<sup>2</sup> Beitr. z. path. Anat. u. z. allg. Path., 1909, XLII, 248.

<sup>3</sup> Centralbl. f. allg. Path. u. path. Anat., 1914, XXV, 865.

## REFLEXES.

	R.	L.	Remarks.
Triceps .....	+	+++	
Abdominal .....	—	—	
Cremasteric .....	—	—	
Patellar .....	+	+	equal.
Plantar .....	+	+	equal.

There was no Babinski or Kernig reaction; urination and the passing of feces occurred involuntarily; the eye-grounds were not examined.

*Autopsy.*—The body was that of a well-nourished negro about 65 years old, well-developed, symmetrical, with no evidence of atrophy. Briefly, there were no changes of note in the trunk viscera other than a moderate pulmonary emphysema, a rather marked general arteriosclerosis and a cloudy swelling of the various parenchymatous organs.

There were no changes of note in the pericranial tissues. The skull was well formed and relatively thin, as a result to pressure atrophy of the internal table. The dura was firmly adherent along the sagittal suture, the cerebral convolutions were flattened, the leptomeninges somewhat oedematous and their vessels engorged. There was no gross asymmetry of the cerebral cortex and the hypophysis and sella turcica were unchanged. There was bilateral internal-hydrohemocephalus and the cavum of the left lateral ventricle contained about 20 cc. of a semisanguineous fluid in which floated a few minute dark-brown floccules. The choroid plexus of this side and macroscopically all portions of the ependymal surface were normal.

In the right lateral ventricle there was a roughly egg-shaped tumor almost completely filling the distorted ventricle and measuring 4.7 x 2.5 x 3.5 cm. Its outer surface was covered with a dense proliferation of short, delicate, very friable papillae, and the ventricle contained a considerable amount of flocculent debris, detached necrotic papillae and fragments of old blood-clot. The choroid plexus entered directly into the tumor, forming a distinct pedicle, the only point of attachment of the growth. The tumor could be lifted free from the cavum of the ventricle. The ependymal surface of the ventricle was roughened from pressure necrosis, and covered with a thin film of blood-coagulum in various stages of organization. The pedicle of choroid plexus presented a compensatory hypertrophy and was four or five times its normal size. When sectioned, macroscopically, the tumor was found to consist mainly of a matrix of more or less spherical islands of cartilage 1 to 2 or 3 mm. in their greatest diameters. In part these nodules were multilobulated.

Tissues were fixed in both 10 per cent formalin and Zenker's fluid, and embedded in both paraffin and celloidin. Sections were stained with hematoxylin and eosin, Mallory's phosphotungstic-acid hematoxylin, Weigert's neuroglia stain, and safranin. Microscopically, the papillae are found to possess a multilayered epithelium. The basal layer consists of low columnar epithelium having a distinct palisade arrangement and being sharply defined from the superimposed layers, the cells of which are markedly flattened. The cell outlines are indistinct, the upper cell layers appearing more as a syncytial



mass. The nuclei of the lower layers stain deeply and are plump, vesicular and centrally located. The nuclei of the upper cell layers are very much flattened and distorted. The basal portions of the crypts between papillæ are frequently completely filled with the epithelium. The older layers of the central portions of these alveoli are not infrequently necrotic, forming a pseudoglandular structure filled with granular cell-débris. They resemble very much the so-called cylindromata of the brain except that the pseudolumina contain a granular and not a hyaline-appearing substance. In the neighborhood of the necrotic areas, which frequently are strikingly regular in outline, the cell nuclei are markedly pycnotic. The cytoplasm of the cells stains with varying grades of eosin to almost a bright carmine, the most brilliant eosin appearing in the most markedly degenerated areas. The epithelial cytoplasm is very finely granular, and non-vacuolated. There is no evidence of any tendency to hyaline epithelial degeneration. In the degenerated portions the nuclei undergo a finely granular fragmentation by karyorrhexis. Occasionally the cells of an entire alveolus are seen to be necrotic, or a group of alveoli have undergone necrosis. There is no evidence of an infiltrative growth. Mitotic figures are very few; not more than one in 60 to 100 fields are found. Weigert's neuroglia and Mallory's phosphotungstic-acid hematoxylin stains reveal no tendency to the formation of neuroglia fibrils, as is sometimes seen in the epithelium of true ependymomata. The stroma of the papillæ consists of a finely fibrillar, apparently oedematous, connective tissue, whose cells are polygonal, branching and occasionally vesicular.

In those planes in which the papillary blood vessels have been met with, the blood space is centrally located and separated from the adjacent stroma by only its endothelial lining. Ir-

regular necrotic areas are frequently found in the stroma of the body of the tumor. These consist of an eosin-staining granular débris and usually contain small calcareous granules with a typical concentric lamellation ("brain sand").

The body of the tumor consists for the greater part of islands of typical hyaline cartilage, each island having a definite perichondrium of more compact connective tissue than that of the stroma generally. The cartilage throughout is intact, with no tendency toward necrosis or calcification.

I have not been able to find a similar choroid-plexus tumor described. The growth, it would seem, can best be classified as a mixed tumor—a teratoma, the mesoblastic cartilaginous elements of which were carried in at the time of the embryonic pushing-in of the velum interpositum of the brain, leading in part to the formation of the choroid plexus. That we are dealing with a pure fibro-epithelial tumor with a metaplastic transformation of its connective tissue to cartilage would seem less likely.

#### EXPLANATION OF FIGURES.

FIG. 1.—Section through both cerebral cortices. The section of the left cortex was made at a level 2 cm. below that of the right cortex. The section through the right cortex also passes through the tumor in a plane at the juncture of its upper and middle thirds, leaving its pedicle-like attachment to the choroid plexus intact.

FIG. 2.—Islands of hyaline cartilage composing the greater portion of the body of the tumor. A. Cross-section of a small epithelial nest. Magnification 1-20.

FIG. 3.—Section from periphery of tumor where its epithelial elements predominate. Magnification 1-40.

FIG. 4.—Epithelium at the bottom of a crypt between two papillæ. A. Calcium granules in necrotic stroma. Magnification 1-150.

## A CASE OF HEART-BLOCK WITH RECOVERY.

By E. W. BRIDGMAN, M. D., and JOHN T. KING, JR., M. D.

(From the Medical Clinic of The Johns Hopkins Hospital.)

Initiated by Erlanger and constantly stimulated by Hirschfelder, Barker, Thayer and Peabody, the interest of The Johns Hopkins Hospital in the study of heart-block has contributed to the advancement of the knowledge of this condition. Although a great number of cases of His bundle lesions, in many of which the clinical findings were substantiated by autopsy, have been reported, there have been few instances of complete block with Adams-Stokes syndrome, with complete recovery following therapy. On this account, and because of interesting observations which developed during the physiological studies of the patient, the following case is put on record:

Willie Howard, aged 38, colored, married, engaged as an active day-laborer, was admitted to the medical service of the hospital on October 8, 1914, complaining of "spells of dizziness and weakness." Except for the fact that his wife has had two miscarriages and two babies dying at birth, the family history is irrelevant. Besides the usual exanthemata, the patient had diphtheria as a

child and small-pox four years before admission—both with no untoward effects. There is a history of rare attacks of tonsillitis. Following a urethritis 10 years before admission and persisting, with winter relapses, up to the present illness, there have been arthritic symptoms—painful and stiff joints, but without fever or swelling. In past years there have been occasional brief attacks of a feeling of tightness in the epigastrium, associated with dyspnœa, faintness, and dizziness. Recently these symptoms have been much less frequent, and apparently bear no relation to the present condition. Only rarely has palpitation been noted. The patient denies primary luetic lesion or secondary manifestations. He is markedly alcoholic, drinking whiskey, gin and beer to the point of intoxication.

The present illness dates from September 29, nine days before admission, when, while hard at work, he was seized with a "kind of chill." His head and body ached, he was dizzy and nauseated, became extremely weak, and had palpitation and dyspnœa. At this time there was a syncopal attack lasting two minutes. He soon resumed his work and had no further symptoms until the following day, when he became so weak that he was forced to go home. Here he remained until entering the hospital. He has had dizzy spells and syncopal attacks similar to the initial seizure, at





FIG. 1.

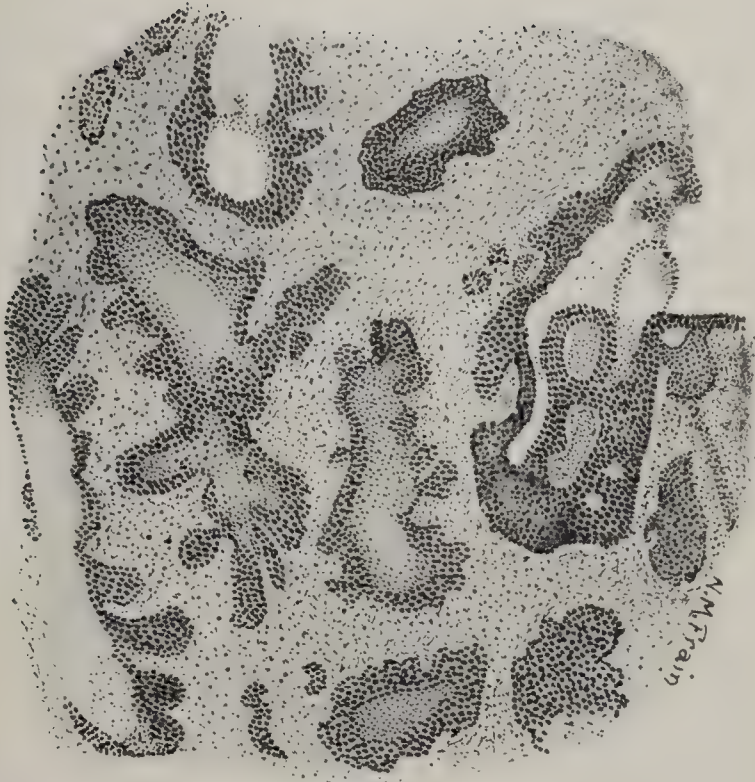


FIG. 3.

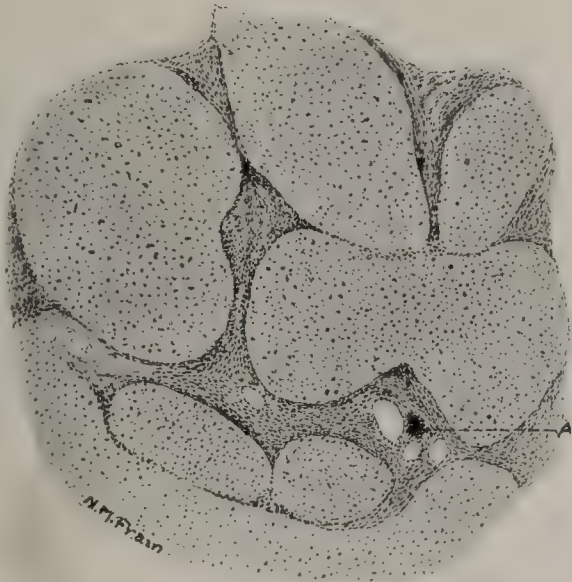


FIG. 2.

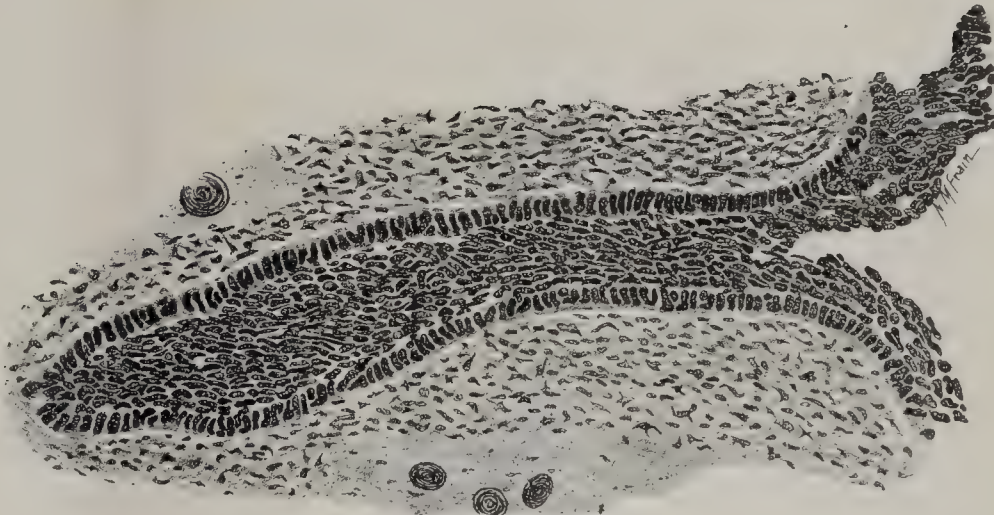


FIG. 4.



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intervals of two or three days. There have been no further symptoms of cardiac insufficiency.

On October 5, three days before admission, while he was a patient in one of the other services, the pulse was 88, whereas eighteen hours later it was 32 to the minute. With this bradycardia, auscultation at the apex disclosed a systolic whiff with soft, short sounds, generally two or three in number, between the ventricular sounds. The soft beats were synchronous with visible jugular pulsations, and were not manifest at the wrist, where the ventricular systoles were readily palpable. During the following two days there were several dizzy spells, without syncope, in which the pulse-rate varied from 24 to 88. On October 7, although no signs of decompensation had appeared, the patient was given fifteen minims of the tincture of digitalis after each meal. During the night he had numerous dizzy spells but without syncope. On the following morning he again received 15 minims of the tincture of digitalis, and was admitted to the medical service before noon.

At that time he was quite conscious and normally oriented. His temperature was 97°; the respirations were 32. He appeared extremely ill, and was pale and cyanotic. His hands and feet were cold and clammy. There was outspoken Cheyne-Stokes breathing, whose cycle was about one minute. The eye-balls were rolled, coordinately but purposelessly. The pupils were slightly irregular but normally active. No nystagmus was observed. At times there appeared a divergent squint when the eyes were at rest. The tonsils were small and apparently clean. The jugular veins were distended and showed distinct, single-crested pulsations in groups of from seven to ten, in regular succession, between each carotid pulsation. There were about one hundred and ten venous waves per minute. There was no general glandular enlargement. The thorax was not remarkable on inspection and the lungs gave normal findings.

There was no precordial bulge. The point of maximum impulse was in the 4th interspace, in the nipple line and 9.5 cm. from the mid-sternal line. The relative cardiac dulness began above at the 2d interspace and reached 1.5 cm. to the right and 11.5 cm. to the left of the median sternal line. There was no retro-manubrial dulness. At the apex, the ventricular sounds were of normal intensity, and were accompanied by a systolic murmur. Between these normal cardiac sounds, which occurred from sixteen to twenty times per minute and were synchronous with the radial pulsations, there were distant, tapping sounds heard in regular sequence at about 110 beats to the minute. There was no constant relationship between these soft, tapping sounds, presumably of auricular origin, and the ventricular systoles, and these faint sounds were synchronous with the visible jugular pulsations and had no counterparts at the wrist. They were best heard in the 3d and 4th left interspaces near the sternum, were audible at the apex and barely heard at the aortic area. A pulmonic systolic murmur was present.

The radial pulse was of small volume, low tension, and was absolutely irregular. The vessel walls were not sclerotic. The systolic blood pressure was 108, diastolic, 50. The abdominal examination showed nothing but a palpable, and slightly tender, liver, that reached to the level of the umbilicus in the mid-clavicular line and presented a sharp edge. No genital scar was observed, but there was a thick urethral discharge which subsequently showed numbers of gonococci. There was no oedema.

During examination the patient had a syncopal attack of one minute's duration. It was preceded by a feeling of weakness and dizziness, with pain in the back of the neck. This was soon followed by convulsive movements and unconsciousness, without loss of sphincter control. During this short period the pulse-rate at the wrist rose to 44 per minute, which was maintained for about five minutes. There was marked engorgement of the veins of the face and neck, accompanied by suffusion and sweat. After the attack the patient resumed the condition described in the physical examination.

The blood count and hæmoglobin were not remarkable. The blood culture was later reported negative.

The eye grounds were interesting. The vessels were normal, with no surrounding hæmorrhage or exudate. Both discs were clearly outlined. The veins were full and, in the left eye, one large vein, where it crossed the disc, showed pulsations that were synchronous with ventricular systoles. The auricular beats caused no visible waves. In ventricular diastole the vein became gradually depleted, until it was entirely empty at the point where it crossed the disc, but it filled rapidly during ventricular systole.

The urine on admission was of a specific gravity of 1.025, and showed a faint trace of albumin with numerous hyaline casts and pus cells. Except for the gradual disappearance of the albumin and casts and a lowering of the specific gravity to 1.015, the urinary findings were not remarkable.

The clinical diagnosis was made of complete heart-block with Adams-Stokes syndrome and myocardial insufficiency, probably due to gumma of the septum. It was thought that the condition had been aggravated by digitalis. The patient was, therefore, put absolutely at rest, and allowed a restricted diet and a fluid intake of 1200 cc. With the purpose of increasing coronary circulation, 20 grains of diuretin were given four times a day. Potassium iodide in 50-grain doses was given three times a day and later, following the report of a strongly positive Wassermann reaction, mercurial inunctions were instituted.

Immediately after the admission examination, an electrocardiogram was taken in the three derivations. There is complete heart-block with an irregular ventricular rate that is sometimes as slow as one beat in eleven seconds, although there are never less than sixteen beats per minute. The auricular beats are normal and regular at 105 to the minute. The ventricular complexes are constant in the different derivations. There is a progressive decrease in the heights of the R and T waves from the first to the third derivations. In the third derivation, shown in Fig. 1, the R and T waves are inverted and the P wave is diphasic.

The patient was then given 1/80 grain of atropin in an effort to paralyze the vagus terminals and thereby obviate any digitalis effect on the conduction in the His bundle. There was a slight transitory increase of the ventricular activity, with but little effect on the auricular rate. Shortly afterwards a long electrocardiographic film was taken to show the heart rate in the different periods of the Cheyne-Stokes respiratory cycles. A portion of the tracing is shown in Fig. 2, where an electrocardiogram, in the second derivation, makes evident a marked increase in the ventricular rate during apnoea, and a slowing during dyspnoea, while the auricular rate decreases from a dyspnoeic rate of 100 to an apnoeic rate of 90. The progressive increase in the heights of the P waves up to the time of ventricular systole is interesting. During ventricular diastole the auricles are contracting against steadily increasing resistance, which is relieved by the next ventricular systole.

During the first twenty-four hours after admission the patient had about fifteen brief syncopal attacks resembling the one described. In one of them he fell out of bed.

At noon of the following day (October 9th), associated with malaise and a tonsillar exudate, the temperature became suddenly elevated to 104.6° F. The temperature, although falling steadily from this height, maintained a range from 98°-100° throughout his stay in the hospital. On subsequent observations, it was continuously normal. No further phenomena were found in connection with the fever. On this day, October 9, there was a transitory period which, from observation of the spacing of the heart sounds, and the character of the jugular and radial pulsations, appeared to be a 3-1 partial block. At this time the radial and apical ventricular rates were equal, regular, 44 to the minute. The sounds at the apex suggested two auricular beats between each ventricular systole and one associated auricular and ventricular systole. The



jugular showed pulsations that apparently were synchronous with the auricular sounds at a rate of 132 to the minute. This observation was not checked by an electrocardiogram and the previous rhythm was soon resumed.

On the next day (October 10) the electrocardiogram showed complete block. On this film appeared the only premature ventricular contraction observed in all the tracings, after the preliminary irregularity had disappeared. The ventricular rate had become approximately regular soon after admission when the Cheyne-Stokes respiration ceased. This "extra systole" appeared quite comparable in form to the other ventricular complexes, and suggests a premature beat arising in or near the pace-maker of the idio-ventricular rhythm.

The following day (October 11) the patient was sufficiently improved so that simultaneous apex, venous, and electrocardiographic tracings could be taken. In Fig. 3 one of these tracings is shown with a magnet marking synchronous points on the different curves. On the apex tracing appear auricular waves corresponding to those of the jugular vein. The size of the auricular waves in the neck depends evidently on the phase of ventricular activity. The tracings are characteristic of complete block, but with a ventricular rhythm that, while perfectly regular, is about 50 to the minute.

A note on the clinical history five days later describes the patient as being much improved, bright and comfortable. His liver was no longer tender and had receded to the costal margin. He had had no syncopal attacks since the day after admission. The cardiac examination showed apparently two auricular beats to one ventricular contraction, but with complete dissociation. The electrocardiogram confirmed the clinical findings, demonstrating complete heart-block with a ventricular rate that is regular at 40, and an auricular rate at 80 per minute.

Mercurial inunctions were stopped at this date because of an incipient salivation, but the potassium iodide was continued as before. On the evening of this day partial block was observed clinically, with an auricular beat midway between successive ventricular systoles. The ventricular rate was 49 per minute. The original picture of complete dissociation was resumed in half an hour. There were several periods of partial association in the next few days, and on the 18th this had become constant, and electrocardiograms were obtained. The second derivation is shown in Fig. 4, and demonstrates a two to one block. There is a progressive decrease in the size of the R waves with inverted  $R_s$  and  $T_s$  and with diphasic  $P_s$ . A venous tracing taken three days later (October 21) showed what was apparently a continuation of the two to one partial block, with a ventricular rate of 45 per minute. The "v" and alternate "a" waves coincided to give an abrupt, tall rise after the "c" wave. There had been no changes in the clinical findings.

On the morning of October 23 Professor Thayer made the following note: "As one listens at the apex and just inside, three sounds are heard that are almost equidistant. The first is distant and like a murmur, the second is the first, and the third the second sound of the heart. The three sounds can be timed by placing the finger on the jugular pulse which shows three distinct waves." His impression was that there was still a typical picture of two to one partial block.

In the evening of this same day the pulse became irregular. At the apex were heard rapid, sharp, snapping sounds in groups of from three to sixteen, and the auricular sounds were no longer made out. Very soon the heart became regular, the sharp sounds were superseded by soft sounds of normal quality, and the heart assumed a rate of 80 per minute with no abnormal sounds, beyond a short, apical murmur. Clinically, the evidence of heart-block had disappeared and on the following morning the electrocardiogram confirmed this opinion. There was one to one association, with a rate of 80 per minute. The P R interval was .37 sec.

The patient left the hospital on November 2, with no symptoms beyond a little weakness. The pulse-rate was 100, and the temperature normal. The lungs were clear. The heart showed a decrease in the area of relative dullness as compared with the findings on admission; for it now measured 2 cm. to the right, and 9.5 cm. to the left of the mid-sternal line. At the apex the second sound was louder than the first. The soft systolic murmur persisted, but was heard only at the apex. The pulmonic and aortic second sounds were both accentuated but equal. There were no signs of myocardial insufficiency. The Wassermann reaction was still strongly positive.

Throughout the winter the patient was followed in the dispensary. On November 11 the P R interval had fallen to .25 sec. On the 27th the physical examination showed nothing remarkable. The pulse-rate was regular, 80 per minute. On December 8, although he had continued mercury and iodides since his discharge, it was thought wise to institute intravenous salvarsan therapy; he was, therefore, readmitted to the ward, and 0.2 gm. of salvarsan were given with no untoward effects. His physical examination was not remarkable except for a presystolic element to the first sound which was noted to the left of the lower sternum, at the level of, and just above, the fifth rib. At the apex the second sound was louder than the first and no systolic murmur was heard. The Wassermann reaction was weakly positive. Simultaneous apex, venous, and electrocardiographic tracings were taken, and were not remarkable, the P R interval being .18 sec. and the a-c time .22 sec., approximately normal. These tracings appear in Fig. 5.

The patient was discharged after three days in the hospital and sent to the medical dispensary. From there he was referred to the luetic clinic for further salvarsan therapy. Owing to a misunderstanding, he received no salvarsan, but continued mercury and iodides for two weeks. At that time he left town and discontinued all medication.

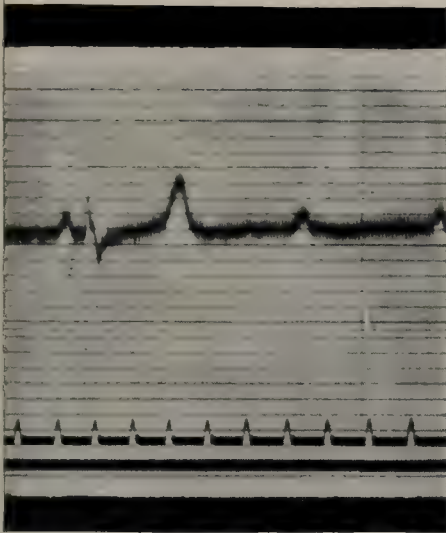
He reappeared in the luetic clinic on March 1, 1915, five months after his first admission to the hospital. His Wassermann reaction was found to be negative, but he was put on mercury and iodides. On March 14 apex, venous and electrocardiographic tracings were obtained, and were apparently normal. The P R interval was .18 sec. and the a-c time .22 sec.

On March 26 a careful history was taken and a physical examination was made. No symptoms were elicited beyond a little short-windedness on climbing stairs. It was found that the patient had gained considerable weight. His pulse was 90 and regular. The relative cardiac area was within normal limits. The sounds were clear at the apex, but there was a faint presystolic gallop, audible near the sternum in the fourth left intercostal space. A pulmonic systolic murmur was audible. Otherwise, nothing of significance was made out.

Electrophonograms in heart-block are rare, and, because of the interest therein, these tracings in the case are reported separately. Many of them were taken simultaneously with venous tracings, on which a signal magnet marked synchronous points. In this way the several tracings could be indirectly compared with the simultaneous apex, venous, and electrocardiographic tracings.

On October 10, during the period of complete block, an electrophonogram was taken, and is reproduced in Fig. 6. At this time the ventricles were contracting thirty times a minute and the auricular rate was one hundred and ten. Many observers who have discussed the clinical findings in heart-block have denied the audibility of the auricular sounds. Many others, especially His, Thayer, Hirschfelder, and Lewis, have repeatedly commented on hearing auricular sounds. In this tracing sound representations appear which are checked as occurring at about the summit of the auricular waves on the jugular pulse. From calculations based on the frequency and amplitude of the different waves, these sounds are found to be well within the limits of human audibility; and,





ases from 105 in dyspnœa to 95

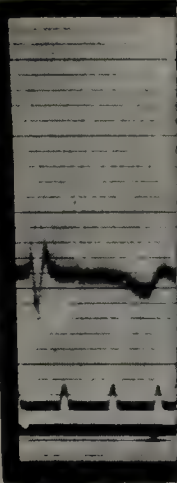
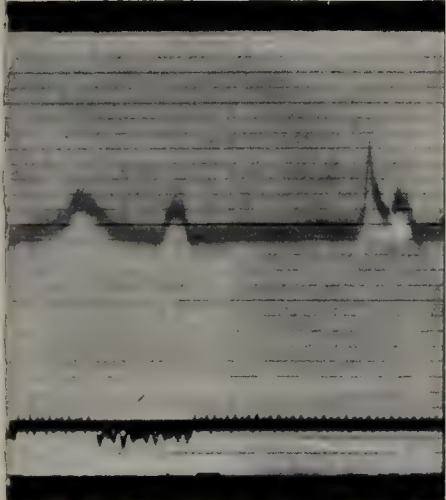


FIG. 1.—Elec



second derivation of the electro  
time interval =  $\frac{1}{5}$  second. Th

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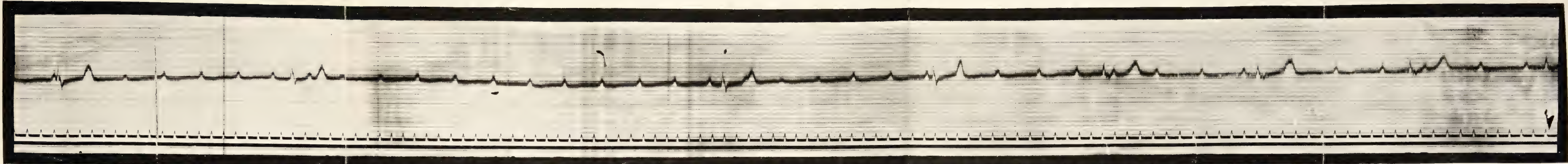


FIG. 2.—Electrocardiogram, second derivation (October 8). Complete heart-block. Progressive increase in the heights of the P waves up to ventricular systole. Auricular rate decreases from 105 in dyspnoea to 95 in apnoea. Ventricular rate is increased markedly during apnoea, and decreased during dyspnoea.

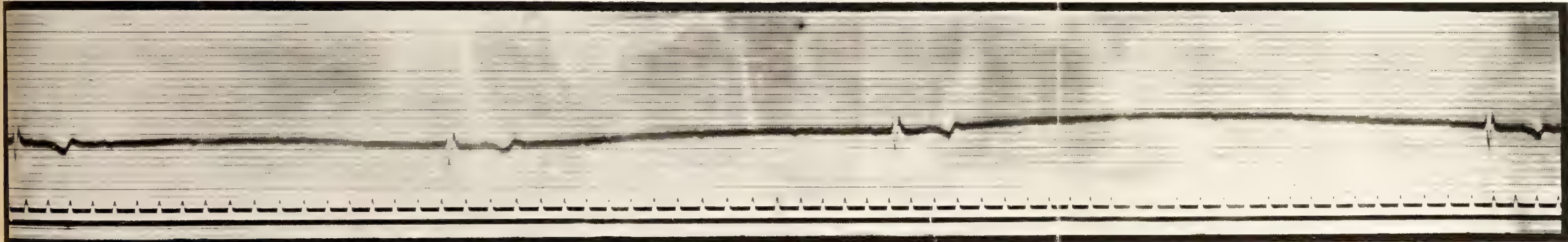


FIG. 1.—Electrocardiogram, third derivation, taken on the day of admission, October 8. Complete heart-block. Auricular rate = 105 per minute and regular. Ventricular rate = 16 per minute and irregular. Note the presence of diphasism or of inversion in the third derivation in all waves: whereas the P, R, and T waves of the first and second derivations were always upright.

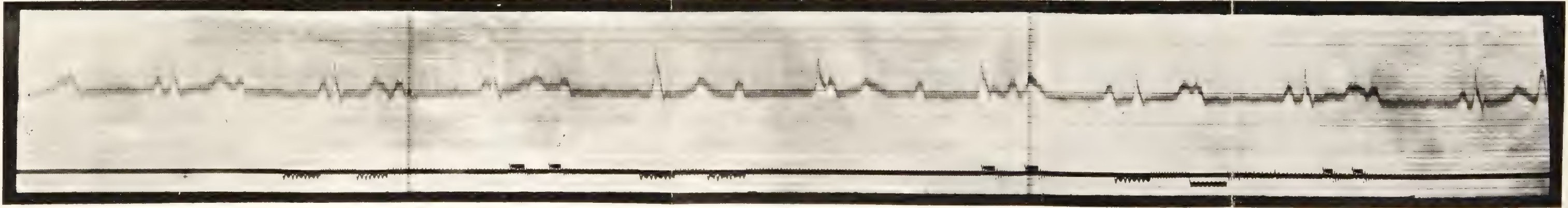
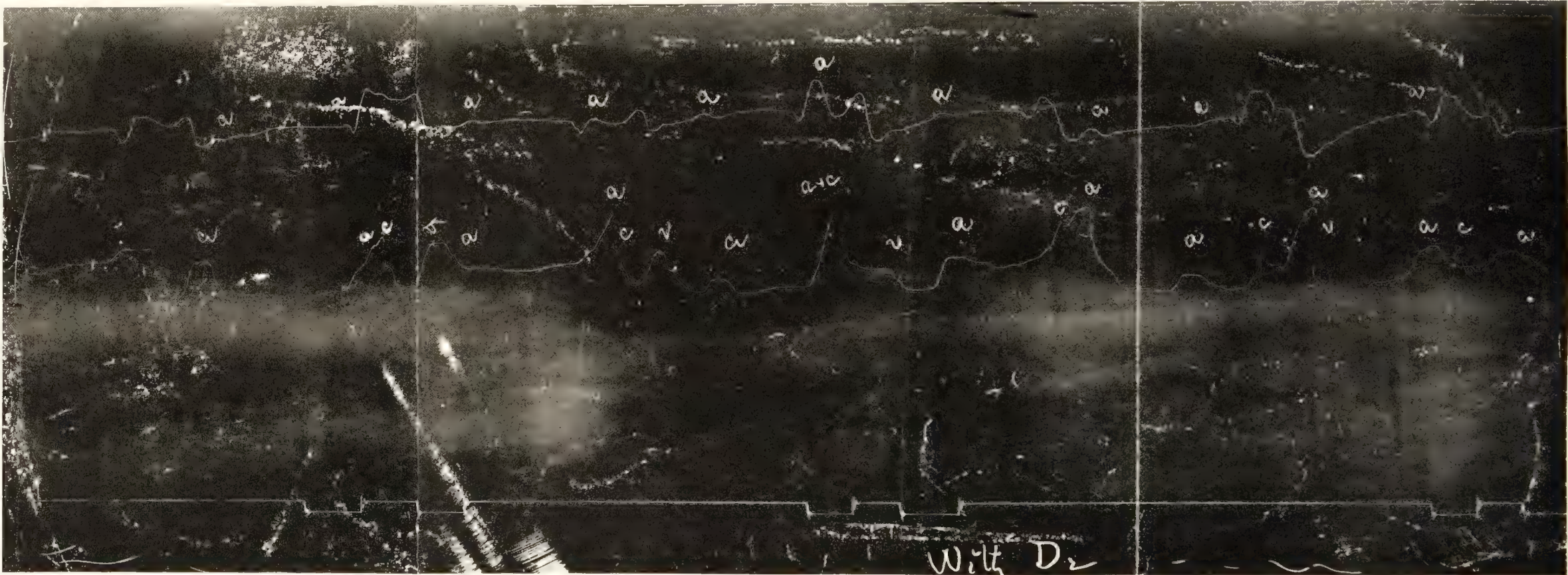


FIG. 3.—Simultaneous apex, venous, and electrocardiographic tracings (October 11). Complete heart-block. The second derivation of the electrocardiogram is shown. The simultaneous signal magnet writes below the base-line in both the polygram and the electrocardiogram. Auricular waves are well recorded in the apex tracing. Time interval =  $\frac{1}{5}$  second. The auricular waves in both the apex and the venous tracing are marked "a."





FIG. 4.—Electrocardiogram, second derivation (October 18), showing a 2:1 partial heart-block.

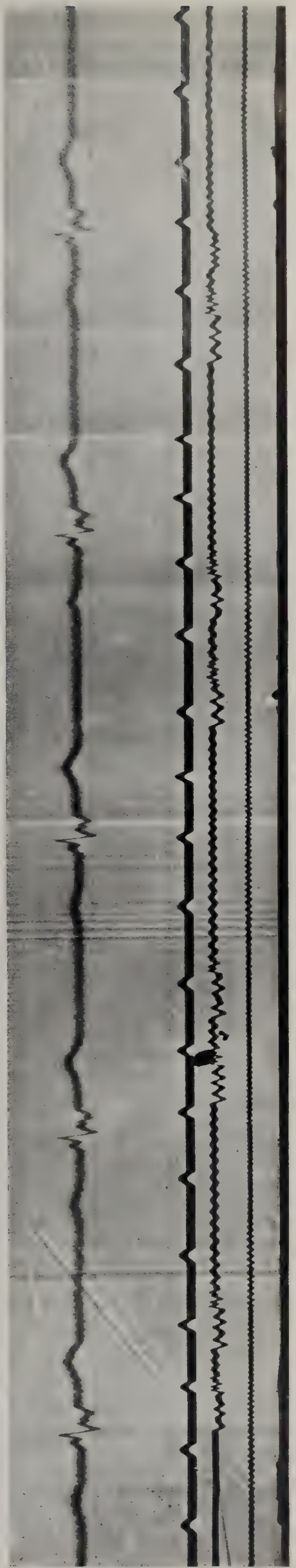
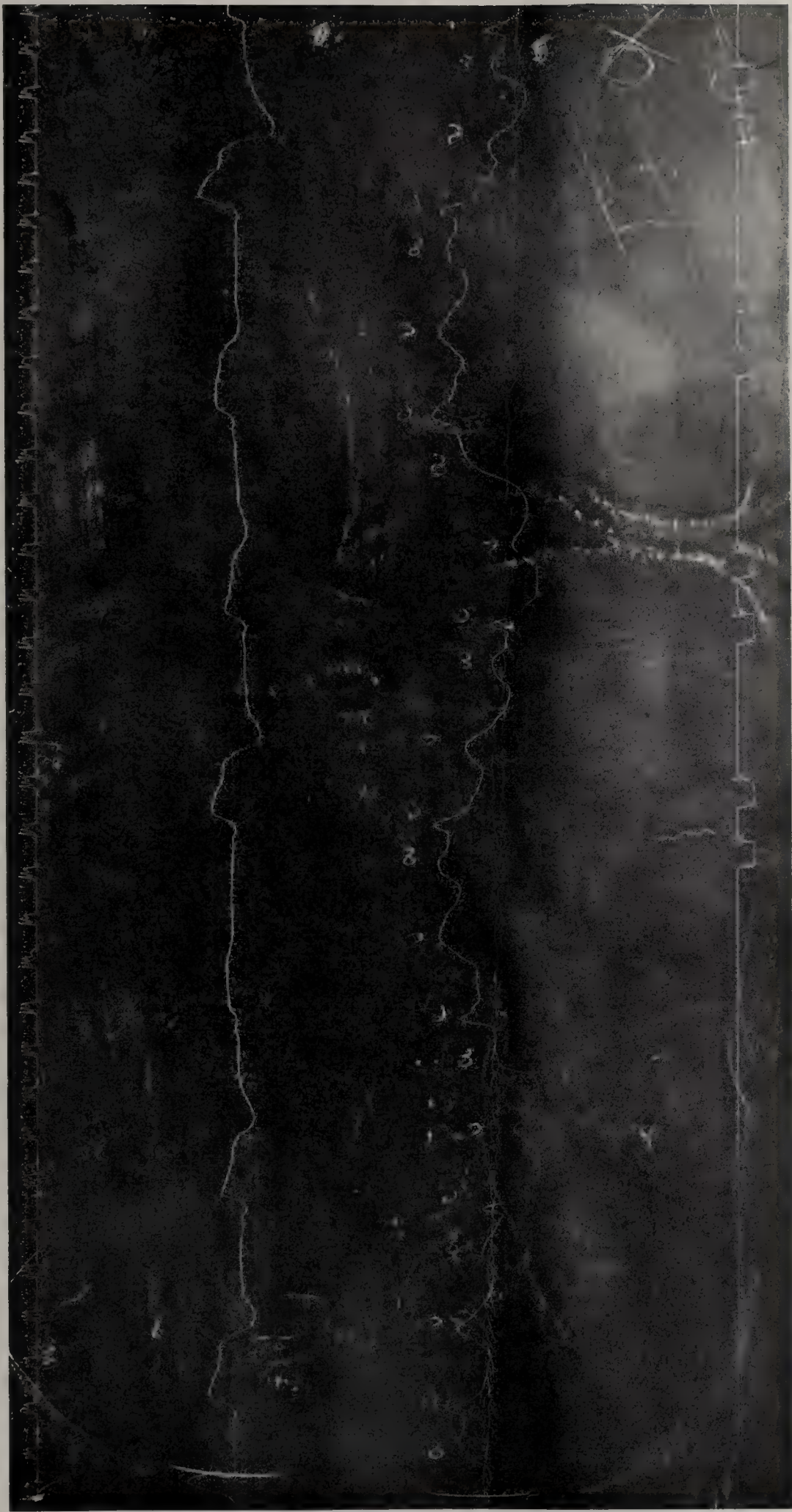


FIG. 5.—Simultaneous apex, venous, and electrocardiographic tracings (December 9). The signal marker records synchronous points. P-R interval = .18 second. a-c time = .22 second. Time interval =  $\frac{1}{5}$  second. Second derivation shown.



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FIG. 6.—Electrophonogram (October 10). Complete heart-block. Auricular and ventricular sounds.  
Auricular rate = 110. Ventricular rate = 30.

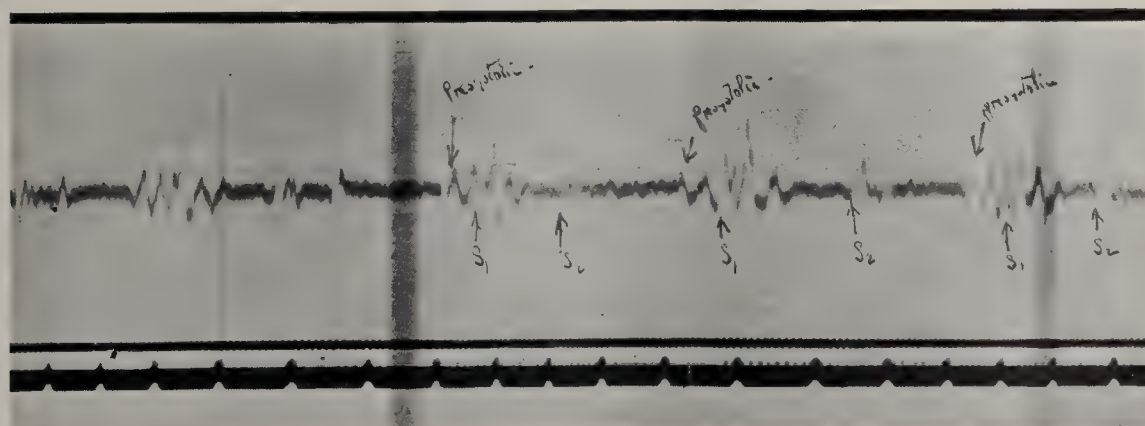
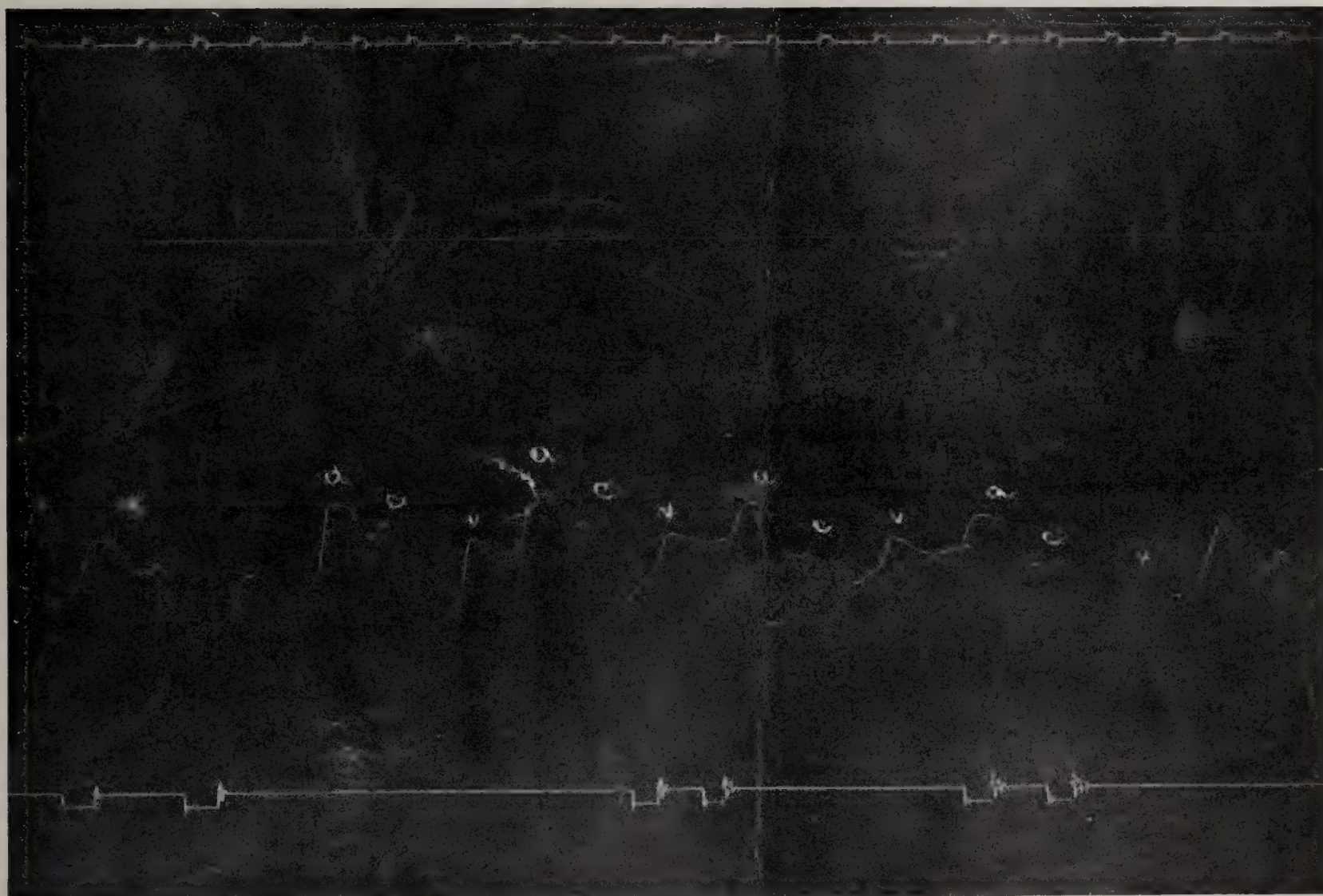


FIG. 7.—Electrophonogram and venous tracing (March 14, 1915). Arrows point to the onset of the sounds. The onset of the first sound is found by measuring .31 second from the beginning of the second sound, which is clearly defined. It should be noted that these measurements give symmetrical points on the phonographic curves.



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moreover, they were heard by the different observers who came in contact with the case. It is interesting that there is no increase in intensity of these auricular sounds corresponding to the increase in height of the P waves of the electrocardiogram, as the auricles contract against increasing resistance during ventricular diastole. It has been held that there are two sounds accompanying auricular contraction, the first due to the actual contraction of the auricular musculature, and the second following the snapping together of the atrio-ventricular valves at the end of the auricular contraction, after blood has been forced into the ventricles. Since the period of auricular contraction, as estimated from the venous tracings and electrocardiograms, is always more than .08 sec. there should be two distinct sounds visible on the electrophonogram, if both of these phenomena were present, whereas in the many films taken there was never any evidence of reduplication of the auricular sounds. (In another case, such double auricular sounds were clearly demonstrated and it would seem that the factors for causing a sound at the end of auricular systole do not always exist.) Furthermore, as far as could be ascertained—and it would seem fair to employ the simultaneous tracings as a basis for comparative measurements—the auricular sounds obtained on the electrophonogram begin constantly within .01-.03 sec. after the onset of auricular systole. In other words, the same time relationship exists between the auricular contraction and the auricular sound, as between the auricular contraction and the presystolic sound of normal individuals. Numerous heart-sound tracings were taken during the patient's stay in the hospital, but nothing of interest appeared until the tracing of December 9. This was at the time of normal rhythm, with a slightly prolonged conduction time. As the actual time of ventricular systole, as measured on the apex tracing, from the onset of ventricular rise to the shoulder is .32 sec., the first sound begins .32 sec. before the second. The onset of the

second sound is clearly seen and the beginning of the first sound can be marked exactly. A presystolic sound occurs .11 sec. before the first sound; that is, at an interval about .02 sec. longer than the normal and thus corresponding to the slightly delayed conduction time. This fact confirms the suggestion that the presystolic sound is of auricular origin. On a subsequent date, March 14, 1915, a similar finding is recorded, and the venous and electrophonographic tracings are shown in Fig. 7. Here in the same way, with a similarly prolonged conduction time, a sound appears .42 sec. before the second sound, while the first sound, according to the apex tracings, begins .31 sec. before the second.

Interesting speculations could be made as to the cause of the great prolongation of the R T time from a normal of about .30 sec. to as much as .70 sec., as to the cause of the increased height of the T waves during the period of complete block, and other phenomena, but it would seem wise to reserve such theoretical observations for some other place.

To summarize, the case is that of a negro man, with complete heart-block, Adams-Stokes syndrome, and a strongly positive Wassermann reaction, who, after antiluetic treatment for a period of less than five weeks, developed practically normal conduction time and became symptomatically well, the Wassermann reaction being negative on two occasions four months later.

Of especial interest is the appearance of electrophonograms which show auricular sounds during complete block, and after normal rhythm had been resumed. The time of the auricular sound is just after the onset of auricular systole, and no sound is apparent at the end of auricular systole.

## VALUABLE ADDITIONS TO THE LIBRARY OF THE JOHNS HOPKINS HOSPITAL BY DR. HOWARD A. KELLY.

During the past year, through the unparalleled liberality of Professor Kelly, upwards of four thousand volumes of books, periodicals, monographs and theses from his private library have been presented to The Johns Hopkins Hospital and placed on the shelves of the library. Many of them, and, in fact, the majority, are books connected with his own special work in gynecology and obstetrics, and represent his zeal as a collector while pursuing his special studies. They include the best treatises upon these important branches of study in German, French and English, and are invaluable for the student of medicine and the physician. They comprise many very rare works also in anatomy, medicine and general surgery, and bear remarkable testimony to the breadth of the donor's interest in the whole science of medicine.

This gift to the hospital emphasizes the need of a building devoted wholly to the use of the library. At present they are crowded into two rooms, already filled, in the Administration Building and are difficult of access. It is most essential to the present use and future development of this library that plans should be made, as speedily as possible, for a new building situated upon the grounds at some site convenient for the use of the hospital staff and the students of the medical school. This building should be large enough to house in fireproof

rooms the various collections now scattered in several separate buildings, and which are subject to the hazard of fire through their proximity to laboratories. This building, in addition to book-rooms and rooms for special study, should have an audience room for medical gatherings and facilities for instruction in the history of medicine and in bibliography. Valuable books at present are being accumulated more rapidly than they can be adequately housed or properly used. Who will be the first to give the hospital this greatly needed addition to its facilities for medical study and investigation?

Anyone who has an opportunity to inspect the books presented by Prof. Kelly cannot fail to be impressed with the magnificence of the contribution which he has made to the hospital.

To show the character of the gift we append below a list of a few of the rare books presented to the library by Dr. Kelly. Each author is chronologically arranged:

Celsus (Aurelius Cornelius): Aurelii Cornelii Celsi medicinae liber primus incipit. Venetiis, 1597. fol.

— De medicina libri octo. In hoc volumine haec continentur: Aurelii Cornelii Celsi medicinae libri viii, quam emendatissimi, graecis etiam omnibus dictionibus restitutis. Quinti Sereni liber de medicina et ipse castigatiss. Accedit index in Celsum, et Serenum sane quam copiosus. Venetiis, 1528. 8°.



- Celsus (Aurelius Cornelius): De re medica libri octo. Accessere in primumejusdem, Hieremiae Thriveri Brachellii commentarii doctissimi [etc.]. Lugd. Bat., 1592. 4°.
- De re medica octo [etc.]. 1608. 32°.
- De medicina libri octo, ex recognitione Joh. Antonidae van der Linden. Editio secunda. Lugd. Bat., 1665. 24°.
- De medicina libri octo, cum praefatione Georg. Wolffg. Wedelii, et indice locupletissimo. Janae, 1713. 16°.
- De medicina libri octo, brevioribus Rob. Constantini, Is. Casauboni aliorumque scholiis ac locis parallelis illustrati. Cura et studio Th. J. ab Almelooven. Patavii, 1722. 16°.
- The same. Ed. ultima. Lugd. Bat., 1730. 16°. Engraved title-page. The same. Lugd. Bat., 1746. 8°. The same. Ed. sec. accurate revisa. Basileae, 1748. 8°. The same. Of medicine. In eight books. Transl. with notes by James Greive. London, 1756. 8°.
- De medicina libri octo ex fide vetustiss. libr . . . et animadversiones auct. tum suas . . . adjecit Car. Christian Krause. Lipsiae, 1766. 8°.
- De re medica libri octo ex fide manuscriptorum. [etc.] recensuit J. Valart. Parisiis, 1772. 16°.
- Ketam [or Ketham] (Joannes de): Fasciculus Medicinae. Incipit fasciculus medicine compositus per excellentissimum artium ac medecine doctorem: dominum Joanem de Ketham Alamannum: tractans de anothomia et diuersis infirmitatibus: et corporis humani: cui annectuntur multi alii tractatus per diuersos excellentissimos doctores compositi. Necnon anothomia Mudini. Gothic letter, double columns, outline woodcuts and fine ornamental initials. Venetiis, 1500. Small fol.
- Avicenna: Liber canonis primus quem princeps Aboali Abinsceni de medicina edidit: translatus a Magistro Gerardo Cremonensi in Toletto ab Arabico in Latinum. Double columns. Venetiis, 1505. 4°.
- Avicennae primi libri fen prima nunc primum per magistrum Jacobum Mantinum medicum Hebraeum ex Hebraico in Latinum translata, et diligentius nuper emendata. Patavii, 1547. 32°.
- Avicennae. Quarta fen primi libri de universali ratione medendi: nunc primum. M. Jacob Mantini medici Hebrei: opera Latinitate donata. Venetiis, 1530. 32°.
- Bound with: Avicennae primi libri fen prima nunc primum per magistrum [etc.]. Patavii, 1547.
- Hippocrates: Magni Hippocratis medicorum omnium facile principis, opera omnia quae extant. Francofurti, 1520. fol.
- Also: Francofurti, 1624.
- Opera . . . per M. Fabium Calvum, Gulielmum Copum, Nicolaum Leonicum, et Andream Brentium . . . latinitate donata. Basileae, 1526. fol.
- Opera, quae ad nos extant omnia, per Janum Cornarium Latina lingua conscripta; nuperrime, post omnes omnium editiones, summa cura emendata. Venetiis, 1546. 4°.
- Opera quae ad nos extant omnia, per Janum Cornarium latina lingua conscripta, et recognita. Cum accessione Hippocratis de hominis structura libri, antea non excusi. Recens illustrata cum argumentis in singulos libros, tum indice insuper copiosissimo, per Joan. Culmannum nunc primum editis. Basileae, 1558. fol.
- Opera quae extant. Graece et Latine . . . scholiis illustrata, a Hieron. Mercuriali . . . 2 v. in 1. Venetiis, 1588. fol.
- Opera omnia ex Jani Cornarii versione una cum Jo. Marinelli commentariis ac Petri Matthaei Pini indice. 3 v. Venetiis, 1737-9. fol.
- Aristoteles: Simplicii commentarii in octo Aristotelis physicae auscultationis libros cum ipso Aristotelis textu. Venetiis, 1526. fol.
- Valescus de Taranta: Philonium. Aureum ac perutile opus practice medicine operam dantibus: quod Philonium appellatur: consummatissimi medici domini Valesci de Tharanta. Novo ac diligenti examine correctum. Introductorius etiam libellus ad practicam medicine partem domini Joannis de Toramira. Lugd., 1526. 12°.
- Argelata (Petrus de): Chirurgia magistri Petri de Largelata. Incipit liber primus Chirurgie magistri Petri de Largelata de bononia artium et medicine doctoris. Venetiis, 1531. fol.
- Galen (Claudius): Opera omnia. 5 v. in 4. Basileae, 1538. fol. Greek text. Edited by Cosseius, Fuchs, and Gemusaeus. At end of v. 5 the book De ossibus is given in Latin. Initial letters said to be by Hans Holbein.
- Opera ex nova Juntarum editione. 9 v. in 5. Venetiis, 1625. fol.
- Omnia quae extant in Latinum sermonem conversa . . . His accedunt nunc primum Con. Gesneri praefatio et prolegomena tripartita, de vita Galeni, ejusque libris et interpretibus. Ex iii. officin. Frobenianae editione. 4 v. Basileae, 1562. fol.
- Date of print, on inside title-pages, 1561.
- Fuchs (Leonhard): De medendis singularum humani corporis partium a summo capite ad imos usque pedes passionibus ac febribus libri quatuor, nunquam antea in lucem editi. Basileae, 1539. 8°.
- Vesalius (Andreas): De humani corporis fabrica libri septem. Basileae, 1543. fol.
- The same. Von des Menschen Corpers Anatomey, ein kurtzer, aber vast nützer Ausszug auss D. A. Vesalij Bücheren, von ihm selbs in Latein beschriben, unnd durch D. Albanum Torinum verdolmetscht. Basel, 1544. fol.
- Epistola, rationem modumque propinandi radicis Chynae decocti, . . . pertractans: et praeter alia quaedam, epistolae cuiusdam ad Jacobum Sylvium sententiam recensens, veritatis ac potissimum humanae fabricae studiosis perutilem: [etc.]. Basileae, 1546. fol.
- Also: Venetiis, 1546. 16°.
- De humani corporis fabrica libri septem. Venetiis, 1568. fol.
- The same. Anatomia: addita nunc postremo etiam antiquorum anatome. Venetiis, 1604. fol.
- Engraved title-page.
- Epitome anatomica. Opus redivivum, cui accessere notae ac commentaria P. Paaw. Lugd. Bat., 1616. 4°.
- Andreae Vesalii Bruxellensis Epitome anatomica. Opus redivivum, cui accessere notae ac commentaria P. Paaw Amstelodamensis in Lugduno Batava Academia Professoris Anatomici. Amstelredami, 1633. 8°.
- Librorum de humanis corporis fabrica epitome, cum annotationibus Nicolai Fontani. Amstelodami, 1642. fol.
- Engraved title-page.
- Opera omnia anatomica et chirurgica, cura Hermannii Boerhaave et Bernhardi Siegfried Albini. 2 v. Lugd. Bat., 1725. fol.
- Engraved title-page.
- Vesalius (Andreas) & de Valverde (Joan): Anatomie, ofte afbeeldinghe van de deelen des menschelijcken lichaems, en derselver verklaringhe. Met een aenwijsinghe om het selve te ontleden, volgens de leeringe Galleni, Vesalii, Fallopii, en Arantii. Amsterdam, 1647. fol.
- Engraved title-page.
- Rhazes (Abu Bekr Muhammad Ben Zeakhariah Alrazi): Abubetri Rhazae Maomethi, ob usum experientiamque multiplicem, et ob certissimas ex demonstrationibus logicis indicationes, ad omnes praeter naturam affectus, atque etiam propter remediorum uberrimam materiam, summi medici opera exquisitiora [etc.]. Basileae, 1544. fol.



de Valverde (Joan): Anatomia del corpo humano composta per . . . e da luy con molte figure di rame, et eruditi discorsi in luce mandata. Roma, 1560. fol.

— Anatomie, oft levende beelden vande deelen des menschelicken lichaems. Met de verclaringhe van dien, inde nederduytsche spraecke. t'Antwerpen, 1568. 4°.

Falloppio (Gabriel): De medicatis aquis atque de fossilibus. Tractatus pulcherrimus, ac maxime utilis: ab Andrea Marcolino Fanestri medico ipsius discipulo amantissimo collectus. Accessit ejusdem Andreae duplex epistola: in quarum altera ad lectorem, et hujus libri inter reliqua utilitas, et docendi modus, ac totius rei, quae in hoc ipso opere continetur, summa breviter explicatur. Cum indice rerum magis observandarum copiosissimo, ac capitum omnium, quae in hoc opusculo tractantur, cathalogo, quem sequens pagina indicabit. Venetiis, 1564. 8°.

— Libello duo, alter de ulceribus: alter de tumoribus praeter naturam. Nunc denuo ab erroribus vindicati, ac in studiosorum gratiam in lucem editi. Secunda editio. Venetiis, 1566. 8°.

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